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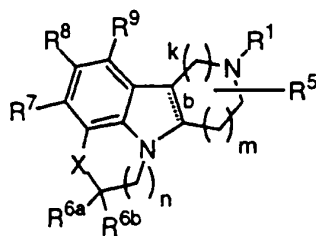
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(54) Title: SUBSTITUTED HETEROCYCLE FUSED GAMMA-CARBOLINES



(I)

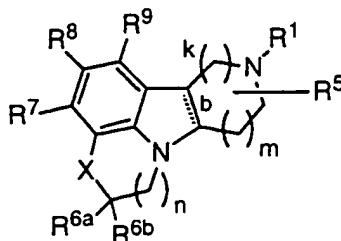
(57) Abstract: The present invention is directed to certain
novel compounds represented by structural Formula (I)
or pharmaceutically acceptable salt forms thereof, wherein
R¹, R⁵, R^{6a}, R^{6b}, R⁷, R⁸, R⁹, X, b, k, m, and n, and the
dashed lines are described herein. The invention is also
concerned with pharmaceutical formulations comprising
these novel compounds as active ingredients and the use
of the novel compounds and their formulations in the
treatment of certain disorders. The compounds of this
invention are serotonin agonists and antagonists and are
useful in the control or prevention of central nervous
system disorders including obesity, anxiety, depression,psychosis, schizophrenia, sleep disorders, sexual disorders, migraine, conditions associated with cephalic pain, social phobias, and
gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility.

TITLE

SUBSTITUTED HETEROCYCLE FUSED GAMMA-CARBOLINES.

FIELD OF THE INVENTION

5 The present invention is directed to certain novel compounds represented by structural Formula (I)



(I)

10 or pharmaceutically acceptable salt forms thereof, wherein R¹, R⁵, R^{6a}, R^{6b}, R⁷, R⁸, R⁹, X, b, k, m, and n, and the dashed lines are described herein. The invention is also concerned with pharmaceutical formulations comprising these novel compounds as active ingredients and the use of the

15 novel compounds and their formulations in the treatment of certain disorders. The compounds of this invention are serotonin agonists and antagonists and are useful in the control or prevention of central nervous system disorders including obesity, anxiety, depression, psychosis,

20 schizophrenia, sleep disorders, sexual disorders, migraine, conditions associated with cephalic pain, social phobias, and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility.

25 BACKGROUND OF THE INVENTION

There exists a substantial correlation for the relationship between 5-HT₂ receptor modulation and a variety of diseases and therapies. To date, three subtypes of the 5-HT₂ receptor class have been identified, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. Prior to the early 1990's the 5-HT_{2C}

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and 5-HT_{2A} receptors were referred to as 5-HT_{1C} and 5-HT₂, respectively.

The agonism or antagonism of 5-HT₂ receptors, either selectively or nonselectively, has been associated with the treatment of various central nervous system (CNS) disorders. Ligands possessing affinity for the 5-HT₂ receptors have been shown to have numerous physiological and behavioral effects (Trends in Pharmacological Sciences, 11, 181, 1990). In the recent past the contribution of serotonergic activity to the mode of action of antidepressant drugs has been well documented. Compounds that increase the overall basal tone of serotonin in the CNS have been successfully developed as antidepressants. The serotonin selective reuptake inhibitors (SSRI) function by increasing the amount of serotonin present in the nerve synapse. These breakthrough treatments, however, are not without side effects and suffer from delayed onset of action (Leonard, J. Clin. Psychiatry, 54(suppl), 3, 1993). Due to the mechanism of action of the SSRIs, they effect the activity of a number of serotonin receptor subtypes. This non-specific modulation of the serotonin family of receptors most likely plays a significant role in the side effect profile. In addition, these compounds often have a high affinity for a number of the serotonin receptors as well as a multitude of other monoamine neurotransmitters and nuisance receptors. Removing some of the receptor cross reactivity would allow for the examination and possible development of potent therapeutic ligands with an improved side effect profile.

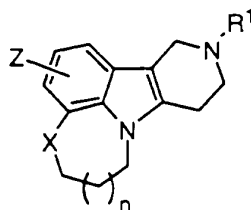
There is ample evidence to support the role of selective 5-HT₂ receptor ligands in a number of disease therapies. Modulation of 5-HT₂ receptors has been associated with the treatment of schizophrenia and psychoses (Ugedo, L., et.al., Psychopharmacology, 98, 45, 1989). Mood, behavior and hallucinogenesis can be affected by 5-HT₂ receptors in the limbic system and cerebral

cortex. 5-HT₂ receptor modulation in the hypothalamus can influence appetite, thermoregulation, sleep, sexual behavior, motor activity, and neuroendocrine function (Hartig, P., et.al., Annals New York Academy of Science, 149, 159). There is also evidence indicating that 5-HT₂ receptors mediate hypoactivity, effect feeding in rats, and mediate penile erections (Psychopharmacology, 101, 57, 1990).

Compounds exhibiting selectivity for the 5-HT_{2B} receptor are useful in treating conditions such as tachygastria, hypermotility associated with irritable bowel disorder, constipation, dyspepsia, and other peripherally mediated conditions.

5-HT_{2A} antagonists have been shown to be effective in the treatment of schizophrenia, anxiety, depression, and migraines (Koek, W., Neuroscience and Behavioral reviews, 16, 95, 1996). Aside from the beneficial antipsychotic effects, classical neuroleptic are frequently responsible for eliciting acute extrapyramidal side effects and neuroendocrine disturbances. These compounds generally possess significant dopamine D₂ receptor affinity (as well as other nuisance receptor affinity) which frequently is associated with extra pyramidal symptoms and tardive dyskinesia, thus detracting from their efficacy as front line treatments in schizophrenia and related disorders. Compounds possessing a more favorable selectivity profile would represent a possible improvement for the treatment of CNS disorders.

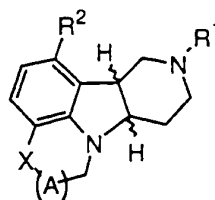
U.S. Patent Numbers 3,914,421; 4,013,652; 4,115,577; 4,183,936; and 4,238,607 disclose pyridopyrrolobenz-heterocycles of formula:



where X is O, S, S(=O), or SO₂; n is 0 or 1; R¹ is various carbon substituents, and Z is a monosubstituent of H, methyl, or chloro.

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U.S. Patent Number 4,219,550 discloses pyridopyrrolo-benzheterocycles of formula:



where X is O or S; R¹ is C₁₋₄ alkyl or cyclopropyl; R² is H, CH₃, OCH₃, Cl, Br, F, or CF₃; and (A) is -CH₂-, -CH(CH₃)-, or -CH₂CH₂-.

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SUMMARY OF THE INVENTION

One object of the present invention is to provide novel compounds which are useful as agonists or antagonists of 5-HT₂ receptors, more specifically 5-HT_{2A} and 5-HT_{2C} receptors, or pharmaceutically acceptable salts or prodrugs thereof.

It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

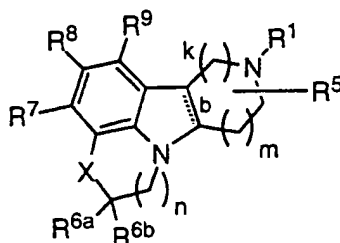
It is another object of the present invention to provide a method for treating central nervous system

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disorders including obesity, anxiety, depression, psychosis, schizophrenia, sleep and sexual disorders, migraine and other conditions associated with cephalic pain, social phobias, and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

More specifically, the present invention provides a method for treating obesity anxiety, depression, or schizophrenia.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of Formula (I):

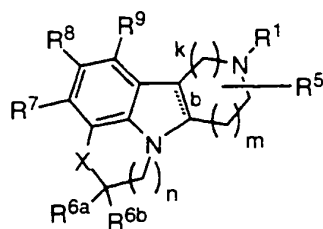


(I)

or pharmaceutically acceptable salt or prodrug forms thereof, wherein R¹, R⁵, R^{6a}, R^{6b}, R⁷, R⁸, R⁹, X, b, k, m, and n are defined below, are effective agonists or antagonists of 5-HT₂ receptors.

DETAILED DESCRIPTION OF THE EMBODIMENTS

Thus, in a first embodiment, the present invention provides a novel compound of Formula (I):



(I)

or stereoisomers or pharmaceutically acceptable salt forms thereof, wherein:

5

b is a single bond or a double bond;

X is $-\text{CHR}^{10}-$, $-\text{C}(=\text{O})-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(=\text{O})-$, $-\text{S}(=\text{O})_2-$,
 $-\text{NR}^{10\text{A}}-$, $-\text{C}(=\text{O})\text{NR}^{10\text{A}}-$, or $-\text{NR}^{10\text{A}}\text{C}(=\text{O})-$;

10

R^1 is selected from

H,

$\text{C}(=\text{O})\text{R}^2$,

$\text{C}(=\text{O})\text{OR}^2$,

15

C_{1-8} alkyl,

C_{2-8} alkenyl,

C_{2-8} alkynyl,

C_{3-7} cycloalkyl,

C_{1-6} alkyl substituted with Z,

20

C_{2-6} alkenyl substituted with Z,

C_{2-6} alkynyl substituted with Z,

C_{3-6} cycloalkyl substituted with Z,

aryl substituted with Z,

5-6 membered heterocyclic ring system containing at

25

least one heteroatom selected from the group

consisting of N, O, and S, said heterocyclic ring

system substituted with Z;

C_{1-3} alkyl substituted with Y,

C_{2-3} alkenyl substituted with Y,

30

C_{2-3} alkynyl substituted with Y,

- C₁₋₆ alkyl substituted with 0-2 R²,
C₂₋₆ alkenyl substituted with 0-2 R²,
C₂₋₆ alkynyl substituted with 0-2 R²,
aryl substituted with 0-2 R², and
5 5-6 membered heterocyclic ring system containing at least one heteroatom selected from the group consisting of N, O, and S, said heterocyclic ring system substituted with 0-2 R²;
- 10 Y is selected from
C₃₋₆ cycloalkyl substituted with Z,
aryl substituted with Z,
5-6 membered heterocyclic ring system containing at least one heteroatom selected from the group
15 consisting of N, O, and S, said heterocyclic ring system substituted with Z;
C₃₋₆ cycloalkyl substituted with -(C₁₋₃ alkyl)-Z,
aryl substituted with -(C₁₋₃ alkyl)-Z, and
5-6 membered heterocyclic ring system containing at least one heteroatom selected from the group
20 consisting of N, O, and S, said heterocyclic ring system substituted with -(C₁₋₃ alkyl)-Z;
- Z is selected from H,
25 -CH(OH)R²,
-C(ethylenedioxy)R²,
-OR²,
-SR²,
-NR²R³,
30 -C(O)R²,
-C(O)NR²R³,
-NR³C(O)R²,
-C(O)OR²,
-OC(O)R²,

- CH(=NR⁴)NR²R³,
-NHC(=NR⁴)NR²R³,
-S(O)R²,
-S(O)₂R²,
5 -S(O)₂NR²R³, and -NR³S(O)₂R²;

- R², at each occurrence, is independently selected from
C₁₋₄ alkyl,
C₂₋₄ alkenyl,
10 C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
phenyl substituted with 0-5 R⁴²,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R⁴¹, and
5-10 membered heterocyclic ring system containing from
15 1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴¹;

- R³, at each occurrence, is independently selected from
20 H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

alternatively, R² and R³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R⁴)-;

- 25 R⁴, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;

R⁵ is H or C₁₋₄ alkyl;

- 30 R^{6a} and R^{6b}, at each occurrence, are independently selected
from
H, -OH, -NR⁴⁶R⁴⁷, -CF₃, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄
alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl,
and

aryl substituted with 0-3 R⁴⁴;

R⁷ and R⁹, at each occurrence, are independently selected from

- 5 H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,
 C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl,
 C₁₋₈ alkoxy, (C₁₋₄ haloalkyl)oxy,
 C₃₋₁₀ cycloalkyl, substituted with 0-2 R³³,
 C₁₋₄ alkyl substituted with 0-2 R¹¹,
 10 C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 5-10 membered heterocyclic ring system containing from
 1-4 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-3
 15 R³¹;

- OR¹², SR¹², NR¹²R¹³, C(O)R¹³, C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
 C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
 NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,
 20 S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², and NR¹⁴S(O)₂R¹²;

R⁸ is selected from

- H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂,
 C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl,
 25 C₁₋₈ alkoxy, (C₁₋₄ haloalkyl)oxy,
 C₃₋₁₀ cycloalkyl, substituted with 0-2 R³³,
 C₁₋₄ alkyl substituted with 0-2 R¹¹,
 C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 30 5-10 membered heterocyclic ring system containing from
 1-4 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-3
 R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)R¹³, C(O)NR¹²R¹³, NR¹⁴C(O)R¹²,
 C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³,
 NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³,
 5 S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², and NR¹⁴S(O)₂R¹²;

R¹⁰ is selected from H, -OH,
 C₁₋₆ alkyl substituted with 0-1 R^{10B},
 C₂₋₆ alkenyl substituted with 0-1 R^{10B},
 10 C₂₋₆ alkynyl substituted with 0-1 R^{10B}, and
 C₁₋₆ alkoxy;

R^{10A} is selected from H,
 C₁₋₆ alkyl substituted with 0-1 R^{10B},
 15 C₂₋₆ alkenyl substituted with 0-1 R^{10B},
 C₂₋₆ alkynyl substituted with 0-1 R^{10B}, and
 C₁₋₆ alkoxy;

R^{10B} is selected from
 20 C₁₋₄ alkoxy,
 C₃₋₆ cycloalkyl,
 C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
 phenyl substituted with 0-3 R³³, and
 5-6 membered heterocyclic ring system containing 1, 2,
 25 or 3 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-2
 R⁴⁴;

R¹¹ is selected from
 30 H, halo, -CF₃, -CN, -NO₂,
 C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl,
 C₁₋₈ alkoxy, C₃₋₁₀ cycloalkyl,
 C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,

aryl substituted with 0-5 R^{33} ,
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
5 R^{31} ;

OR^{12} , SR^{12} , $NR^{12}R^{13}$, $C(O)R^{13}$, $C(O)NR^{12}R^{13}$, $NR^{14}C(O)R^{12}$,
 $C(O)OR^{12}$, $OC(O)R^{12}$, $OC(O)OR^{12}$, $CH(=NR^{14})NR^{12}R^{13}$,
 $NHC(=NR^{14})NR^{12}R^{13}$, $S(O)R^{12}$, $S(O)_2R^{12}$, $S(O)NR^{12}R^{13}$,
10 $S(O)_2NR^{12}R^{13}$, $NR^{14}S(O)R^{12}$, and $NR^{14}S(O)_2R^{12}$;

R^{12} , at each occurrence, is independently selected from
 C_{1-4} alkyl,
 C_{2-4} alkenyl,
15 C_{2-4} alkynyl,
 C_{3-6} cycloalkyl,
phenyl substituted with 0-5 R^{33} ;
 C_{3-10} carbocyclic residue substituted with 0-3 R^{33} , and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
20 R^{31} ;

R^{13} , at each occurrence, is independently selected from
25 H, C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl;

alternatively, R^{12} and R^{13} join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R^{14})-;

30 R^{14} , at each occurrence, is independently selected from H
and C_{1-4} alkyl;

R^{31} , at each occurrence, is independently selected from
H, OH, halo, CF_3 , SO_2R^{45} , $NR^{46}R^{47}$, and C_{1-4} alkyl;

R³³, at each occurrence, is independently selected from
H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, C₁₋₆ alkyl,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₁₋₄
haloalkyl, C₁₋₄ haloalkyl-oxy-, C₁₋₄ alkyloxy-,
5 C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, and C₁₋₄ alkyl-
C(=O)NH-;

R⁴¹, at each occurrence, is independently selected from
10 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN;
C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl
C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴², and
5-10 membered heterocyclic ring system containing from
15 1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴⁴;

R⁴², at each occurrence, is independently selected from
20 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶SO₂R⁴⁵, NR⁴⁶COR⁴⁵,
NR⁴⁶R⁴⁷, NO₂, CN, CH(=NH)NH₂, NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
C₃₋₆ cycloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
25 aryl substituted with 0-3 R⁴⁴, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴⁴;

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R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;

R⁴⁴, at each occurrence, is independently selected from H, halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂, C₁₋₄ alkyl, and C₁₋₄ alkoxy;

5 R⁴⁵ is C₁₋₄ alkyl;

R⁴⁶, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

10 R⁴⁷, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

k is 1 or 2;

15 m is 0, 1, 2, or 3;

n is 0, 1, or 2;

provided when m is 0, then k is 1;

20

provided that when b is a double bond; n is 1 or 2; m is 1; k is 1; X is -O-, -S-, -S(=O)-, or -SO₂-; and the three substituents of R⁷, R⁸, and R⁹, consist of i) three hydrogens, ii) two hydrogens and one chloro, or iii) two
25 hydrogens and one methyl; then R¹ must contain the substituent Z or Y;

provided that when b is a double bond; n is 0 or 1; m is 1; k is 1; X is -CH₂-; and R¹ is hydrogen, C₁₋₆ alkyl or

30 benzyl; then one of R⁷, R⁸, and R⁹, must be other than hydrogen, halo, C₁₋₆ alkyl, C₁₋₆ alkoxy or trifluoromethyl;

provided that when b is a single bond; n is 1 or 2; m is 1; k is 1; X is O or S; and R¹ is C₁₋₄ alkyl or cyclopropyl, then R⁸ is a substituent other than H;

5 provided that when R⁶ or R^{6a} is NH₂, then X is not -CH(R¹⁰); and

provided that when n=0, then R⁶ or R^{6a} is not NH₂ or -OH.

10 In another embodiment of the present invention,

X is -CHR¹⁰-, -C(=O)-, -O-, -S-, -S(=O)-, -S(=O)₂-, -NH-,
-C(=O)NH-, or -NHC(=O)-;

15 R¹ is selected from

H,

C(=O)R²,

C(=O)OR²,

C₁₋₈ alkyl,

20 C₂₋₈ alkenyl,

C₂₋₈ alkynyl,

C₃₋₇ cycloalkyl,

C₁₋₆ alkyl substituted with Z,

C₂₋₆ alkenyl substituted with Z,

25 C₂₋₆ alkynyl substituted with Z,

C₃₋₆ cycloalkyl substituted with Z,

aryl substituted with Z,

5-6 membered heterocyclic ring system containing at least one heteroatom selected from the group

30 consisting of N, O, and S, said heterocyclic ring system substituted with Z;

C₁₋₃ alkyl substituted with Y,

C₂₋₃ alkenyl substituted with Y,

C₂₋₃ alkynyl substituted with Y,

- C₁₋₆ alkyl substituted with 0-2 R²,
C₂₋₆ alkenyl substituted with 0-2 R²,
C₂₋₆ alkynyl substituted with 0-2 R²,
aryl substituted with 0-2 R², and
5 5-6 membered heterocyclic ring system containing at least one heteroatom selected from the group consisting of N, O, and S, said heterocyclic ring system substituted with 0-2 R²;
- 10 Y is selected from
C₃₋₆ cycloalkyl substituted with Z,
aryl substituted with Z,
5-6 membered heterocyclic ring system containing at least one heteroatom selected from the group
15 consisting of N, O, and S, said heterocyclic ring system substituted with Z;
C₃₋₆ cycloalkyl substituted with -(C₁₋₃ alkyl)-Z,
aryl substituted with -(C₁₋₃ alkyl)-Z, and
5-6 membered heterocyclic ring system containing at least one heteroatom selected from the group
20 consisting of N, O, and S, said heterocyclic ring system substituted with -(C₁₋₃ alkyl)-Z;
- Z is selected from H,
25 -CH(OH)R²,
-C(ethylenedioxy)R²,
-OR²,
-SR²,
-NR²R³,
30 -C(O)R²,
-C(O)NR²R³,
-NR³C(O)R²,
-C(O)OR²,
-OC(O)R²,

- CH(=NR⁴)NR²R³,
-NHC(=NR⁴)NR²R³,
-S(O)R²,
-S(O)₂R²,
5 -S(O)₂NR²R³, and -NR³S(O)₂R²;

- R², at each occurrence, is independently selected from
halo,
C₁₋₃ haloalkyl,
10 C₁₋₄ alkyl,
C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
aryl substituted with 0-5 R⁴²;
15 C₃₋₁₀ carbocyclic residue substituted with 0-3 R⁴¹, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴¹;

20

- R³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, and
C₁₋₄ alkoxy;

- 25 alternatively, R² and R³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R⁴)-;

- R⁴, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;

30

- R⁵ is H or C₁₋₄ alkyl;

- R^{6a} and R^{6b}, at each occurrence, are independently selected
from

H, -OH, -NR⁴⁶R⁴⁷, -CF₃, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, and aryl substituted with 0-3 R⁴⁴;

5

R⁷ and R⁹, at each occurrence, are independently selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, (C₁₋₄ haloalkyl)oxy,

10

C₃₋₁₀ cycloalkyl substituted with 0-2 R³³, C₁₋₄ alkyl substituted with 0-2 R¹¹, C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, aryl substituted with 0-5 R³³,

15

5-10 membered heterocyclic ring system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-3 R³¹;

20

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and

25

NR¹²C(O)NHR¹⁵;

R⁸ is selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, (C₁₋₄ haloalkyl)oxy, C₃₋₁₀ cycloalkyl substituted with 0-2 R³³, C₁₋₄ alkyl substituted with 0-2 R¹¹, C₂₋₄ alkenyl substituted with 0-2 R¹¹,

30

C₂₋₄ alkynyl substituted with 0-1 R¹¹,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³,
5-10 membered heterocyclic ring system containing from
5 1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
10 NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,
CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹²,
S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹²,
NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and
NR¹²C(O)NHR¹⁵;

15

R^{10A} is selected from H,

C₁₋₆ alkyl substituted with 0-1 R^{10B},
C₂₋₆ alkenyl substituted with 0-1 R^{10B},
C₂₋₆ alkynyl substituted with 0-1 R^{10B}, and
20 C₁₋₆ alkoxy;

R^{10B} is selected from

C₁₋₄ alkoxy,
C₃₋₆ cycloalkyl,
25 C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
phenyl substituted with 0-3 R³³, and
5-6 membered heterocyclic ring system containing 1, 2,
or 3 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-2
30 R⁴⁴;

R¹¹ is selected from

H, halo, -CF₃, -CN, -NO₂,

- C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl,
 C₁₋₈ alkoxy, C₃₋₁₀ cycloalkyl,
 C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 5 5-10 membered heterocyclic ring system containing from
 1-4 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-3
 R³¹;
- 10 OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
 NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,
 CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹²,
 S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹²,
 NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and
 15 NR¹²C(O)NHR¹⁵;

- R¹², at each occurrence, is independently selected from
 C₁₋₄ alkyl substituted with 0-1 R^{12a},
 C₂₋₄ alkenyl substituted with 0-1 R^{12a},
 20 C₂₋₄ alkynyl substituted with 0-1 R^{12a},
 C₃₋₆ cycloalkyl substituted with 0-3 R³³,
 phenyl substituted with 0-5 R³³,
 C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and
 5-10 membered heterocyclic ring system containing from
 25 1-4 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-3
 R³¹;

- R^{12a}, at each occurrence, is independently selected from
 30 phenyl substituted with 0-5 R³³,
 C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and
 5-10 membered heterocyclic ring system containing from
 1-4 heteroatoms selected from the group

consisting of N, O, and S substituted with 0-3
R³¹;

5 R¹³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

alternatively, R¹² and R¹³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R¹⁴)-;

10 alternatively, R¹² and R¹³ when attached to N may be
combined to form a 9- or 10-membered bicyclic
heterocyclic ring system containing from 1-3
heteroatoms selected from the group consisting of N,
O, and S, wherein said bicyclic heterocyclic ring
15 system is unsaturated or partially saturated, wherein
said bicyclic heterocyclic ring system is substituted
with 0-3 R¹⁶;

R¹⁴, at each occurrence, is independently selected from H
20 and C₁₋₄ alkyl;

R¹⁵, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

25 R¹⁶, at each occurrence, is independently selected from
H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl,
C₁₋₃ haloalkyl-oxy-, and C₁₋₃ alkyloxy-;

30 R³¹, at each occurrence, is independently selected from
H, OH, halo, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, and C₁₋₄ alkyl;

R³³, at each occurrence, is independently selected from
H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-,
C₁₋₄ alkyloxy-,
C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-,
5 C₁₋₄ alkyl-OC(=O)-,
C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆
cycloalkylmethyl-oxy-;
C₁₋₆ alkyl substituted with OH, methoxy, ethoxy,
propoxy, or butoxy; and
10 C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy,
propoxy, or butoxy;

R⁴¹, at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, =O;
15 C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl
C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴², and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
20 consisting of N, O, and S substituted with 0-3
R⁴⁴;

R⁴², at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, SOR⁴⁵, SR⁴⁵, NR⁴⁶SO₂R⁴⁵,
25 NR⁴⁶COR⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, CH(=NH)NH₂,
NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
C₃₋₆ cycloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
30 aryl substituted with 0-3 R⁴⁴, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group

consisting of N, O, and S substituted with 0-3
R⁴⁴;

R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;

5

R⁴⁴, at each occurrence, is independently selected from H,
halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂,
C₁₋₄ alkyl, and C₁₋₄ alkoxy;

10 R⁴⁵ is C₁₋₄ alkyl;

R⁴⁶, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;

15 R⁴⁷, at each occurrence, is independently selected from H,
C₁₋₄ alkyl, -C(=O)NH(C₁₋₄ alkyl), -SO₂(C₁₋₄ alkyl),
-C(=O)O(C₁₋₄ alkyl), -C(=O)(C₁₋₄ alkyl), and -C(=O)H;

k is 1 or 2;

20 m is 0, 1, or 2;

n is 1, 2, or 3;

provided when m is 0 or 1 then k is 1 or 2;

provided when m is 2 then k is 1;

25

provided that when n=0, then R⁶ or R^{6a} is not NH₂ or -OH.

[2] In a preferred embodiment of the present
invention,

30

X is -NR^{10A}-, -C(=O)NR^{10A}-, or -NR^{10A}C(=O)-;

R¹ is selected from

H,

- C(=O)R²,
C(=O)OR²,
C₁₋₈ alkyl,
C₂₋₈ alkenyl,
5 C₂₋₈ alkynyl,
C₃₋₇ cycloalkyl,
C₁₋₆ alkyl substituted with Z,
C₂₋₆ alkenyl substituted with Z,
C₂₋₆ alkynyl substituted with Z,
10 C₃₋₆ cycloalkyl substituted with Z,
aryl substituted with Z,
5-6 membered heterocyclic ring system containing at
least one heteroatom selected from the group
consisting of N, O, and S, said heterocyclic ring
15 system substituted with Z;
C₁₋₃ alkyl substituted with Y,
C₂₋₃ alkenyl substituted with Y,
C₂₋₃ alkynyl substituted with Y,
C₁₋₆ alkyl substituted with 0-2 R²,
20 C₂₋₆ alkenyl substituted with 0-2 R²,
C₂₋₆ alkynyl substituted with 0-2 R²,
aryl substituted with 0-2 R², and
5-6 membered heterocyclic ring system containing at
least one heteroatom selected from the group
25 consisting of N, O, and S, said heterocyclic ring
system substituted with 0-2 R²;

Y is selected from

- C₃₋₆ cycloalkyl substituted with Z,
30 aryl substituted with Z,
5-6 membered heterocyclic ring system containing at
least one heteroatom selected from the group
consisting of N, O, and S, said heterocyclic ring
system substituted with Z;

C₃₋₆ cycloalkyl substituted with -(C₁₋₃ alkyl)-Z,
aryl substituted with -(C₁₋₃ alkyl)-Z, and
5-6 membered heterocyclic ring system containing at
least one heteroatom selected from the group
5 consisting of N, O, and S, said heterocyclic ring
system substituted with -(C₁₋₃ alkyl)-Z;

Z is selected from H,

-CH(OH)R²,
10 -C(ethylenedioxy)R²,
-OR²,
-SR²,
-NR²R³,
-C(O)R²,
15 -C(O)NR²R³,
-NR³C(O)R²,
-C(O)OR²,
-OC(O)R²,
-CH(=NR⁴)NR²R³,
20 -NHC(=NR⁴)NR²R³,
-S(O)R²,
-S(O)₂R²,
-S(O)₂NR²R³, and -NR³S(O)₂R²;

25 R², at each occurrence, is independently selected from
halo,
C₁₋₃ haloalkyl,
C₁₋₄ alkyl,
C₂₋₄ alkenyl,
30 C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
aryl substituted with 0-5 R⁴²;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R⁴¹, and

5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴¹;

5

R³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, and
C₁₋₄ alkoxy;

10 alternatively, R² and R³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R⁴)-;

R⁴, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;

15

R⁵ is H or C₁₋₄ alkyl;

R^{6a} and R^{6b}, at each occurrence, are independently selected
from

20 H, -OH, -NR⁴⁶R⁴⁷, -CF₃, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄
alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl,
and
aryl substituted with 0-3 R⁴⁴;

25 R⁷ and R⁹, at each occurrence, are independently selected
from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,
C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl,
C₁₋₈ alkoxy, (C₁₋₄ haloalkyl)oxy,

30 C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
C₁₋₄ alkyl substituted with 0-2 R¹¹,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³,

5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;

5

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,
CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹²,
S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹²,
10 NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and
NR¹²C(O)NHR¹⁵;

R⁸ is selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂,
15 C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl,
C₁₋₈ alkoxy, (C₁₋₄ haloalkyl)oxy,
C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
C₁₋₄ alkyl substituted with 0-2 R¹¹,
C₂₋₄ alkenyl substituted with 0-2 R¹¹,
20 C₂₋₄ alkynyl substituted with 0-1 R¹¹,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³,
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
25 consisting of N, O, and S substituted with 0-3
R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,
30 CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹²,
S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹²,
NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and
NR¹²C(O)NHR¹⁵;

R^{10A} is selected from H,

C₁₋₆ alkyl substituted with 0-1 R^{10B},

C₂₋₆ alkenyl substituted with 0-1 R^{10B},

5 C₂₋₆ alkynyl substituted with 0-1 R^{10B}, and

C₁₋₆ alkoxy;

R^{10B} is selected from

C₁₋₄ alkoxy,

10 C₃₋₆ cycloalkyl,

C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,

phenyl substituted with 0-3 R³³, and

5-6 membered heterocyclic ring system containing 1, 2,
or 3 heteroatoms selected from the group

15 consisting of N, O, and S substituted with 0-2
R⁴⁴;

R¹¹ is selected from

H, halo, -CF₃, -CN, -NO₂,

20 C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl,
C₁₋₈ alkoxy, C₃₋₁₀ cycloalkyl,

C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,

aryl substituted with 0-5 R³³,

5-10 membered heterocyclic ring system containing from
25 1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,

30 NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,

CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹²,

S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹²,

$\text{NR}^{12}\text{C}(\text{O})\text{R}^{15}$, $\text{NR}^{12}\text{C}(\text{O})\text{OR}^{15}$, $\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{15}$, and
 $\text{NR}^{12}\text{C}(\text{O})\text{NHR}^{15}$;

R^{12} , at each occurrence, is independently selected from
5 C_{1-4} alkyl substituted with 0-1 R^{12a} ,
 C_{2-4} alkenyl substituted with 0-1 R^{12a} ,
 C_{2-4} alkynyl substituted with 0-1 R^{12a} ,
 C_{3-6} cycloalkyl substituted with 0-3 R^{33} ,
phenyl substituted with 0-5 R^{33} ;
10 C_{3-10} carbocyclic residue substituted with 0-3 R^{33} , and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
 R^{31} ;

15 R^{12a} , at each occurrence, is independently selected from
phenyl substituted with 0-5 R^{33} ;
 C_{3-10} carbocyclic residue substituted with 0-3 R^{33} , and
5-10 membered heterocyclic ring system containing from
20 1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
 R^{31} ;

R^{13} , at each occurrence, is independently selected from
25 H, C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl;

alternatively, R^{12} and R^{13} join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R^{14})-;

30 alternatively, R^{12} and R^{13} when attached to N may be
combined to form a 9- or 10-membered bicyclic
heterocyclic ring system containing from 1-3
heteroatoms selected from the group consisting of N,
O, and S, wherein said bicyclic heterocyclic ring

system is unsaturated or partially saturated, wherein said bicyclic heterocyclic ring system is substituted with 0-3 R¹⁶;

5 R¹⁴, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

R¹⁵, at each occurrence, is independently selected from H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

10

R¹⁶, at each occurrence, is independently selected from H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₃ haloalkyl-oxy-, and C₁₋₃ alkyloxy-;

15

R³¹, at each occurrence, is independently selected from H, OH, halo, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, and C₁₋₄ alkyl;

20 R³³, at each occurrence, is independently selected from H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-, C₁₋₄ alkyloxy-, C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-,
25 C₁₋₄ alkyl-OC(=O)-, C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆ cycloalkylmethyl-oxy-;
C₁₋₆ alkyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy; and
30 C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy;

R⁴¹, at each occurrence, is independently selected from H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, =O;

C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl
C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴², and
5 5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴⁴;

R⁴², at each occurrence, is independently selected from
10 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, SOR⁴⁵, SR⁴⁵, NR⁴⁶SO₂R⁴⁵,
NR⁴⁶COR⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, CH(=NH)NH₂,
NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
C₃₋₆ cycloalkyl,
15 C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴⁴, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
20 R⁴⁴;

R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;

R⁴⁴, at each occurrence, is independently selected from H,
25 halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂,
C₁₋₄ alkyl, and C₁₋₄ alkoxy;

R⁴⁵ is C₁₋₄ alkyl;

30 R⁴⁶, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;

R⁴⁷, at each occurrence, is independently selected from H, C₁₋₄ alkyl, -C(=O)NH(C₁₋₄ alkyl), -SO₂(C₁₋₄ alkyl), -C(=O)O(C₁₋₄ alkyl), -C(=O)(C₁₋₄ alkyl), and -C(=O)H;

5 k is 1 or 2;

m is 0, 1, or 2;

n is 1, 2, or 3;

10

provided when m is 0 or 1 then k is 1 or 2;

provided when m is 2 then k is 1;

15 provided that when n=0, then R⁶ or R^{6a} is not NH₂ or -OH.

[3] In a further preferred embodiment of the present invention,

20 X is -NR^{10A}-, -C(=O)NH-, or -NHC(=O)-;

R¹ is selected from

H,

C(=O)R²,

25

C(=O)OR²,

C₁₋₈ alkyl,

C₂₋₈ alkenyl,

C₂₋₈ alkynyl,

C₃₋₇ cycloalkyl,

30

C₁₋₆ alkyl substituted with 0-2 R²,

C₂₋₆ alkenyl substituted with 0-2 R²,

C₂₋₆ alkynyl substituted with 0-2 R²,

aryl substituted with 0-2 R², and

5-6 membered heterocyclic ring system containing at least one heteroatom selected from the group consisting of N, O, and S, said heterocyclic ring system substituted with 0-2 R²;

5
R², at each occurrence, is independently selected from
F, Cl, CH₂F, CHF₂, CF₃,
C₁₋₄ alkyl,
C₂₋₄ alkenyl,
10 C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
phenyl substituted with 0-5 R⁴²;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R⁴¹, and
5-10 membered heterocyclic ring system containing from
15 1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴¹;

R⁵ is H, methyl, ethyl, propyl, or butyl;
20
R^{6a} is selected from
H, -OH, -NR⁴⁶R⁴⁷, -CF₃,
C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, and
aryl substituted with 0-3 R⁴⁴;

25
R^{6b} is H;

R⁷ and R⁹, at each occurrence, are independently selected
from
30 H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,
C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl,
C₁₋₈ alkoxy, (C₁₋₄ haloalkyl)oxy,
C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
C₁₋₄ alkyl substituted with 0-2 R¹¹,

C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 5-10 membered heterocyclic ring system containing from
 1-4 heteroatoms selected from the group
 5 consisting of N, O, and S substituted with 0-3
 R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
 NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,
 10 CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹²,
 S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹²,
 NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and
 NR¹²C(O)NHR¹⁵;

15 R⁸ is selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂,
 C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl,
 C₁₋₈ alkoxy, (C₁₋₄ haloalkyl)oxy,
 C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
 20 C₁₋₄ alkyl substituted with 0-2 R¹¹,
 C₂₋₄ alkenyl substituted with 0-2 R¹¹,
 C₂₋₄ alkynyl substituted with 0-1 R¹¹,
 C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 25 5-10 membered heterocyclic ring system containing from
 1-4 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-3
 R³¹;

30 OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
 NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,
 CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹²,
 S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹²,

$\text{NR}^{12}\text{C}(\text{O})\text{R}^{15}$, $\text{NR}^{12}\text{C}(\text{O})\text{OR}^{15}$, $\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{15}$, and
 $\text{NR}^{12}\text{C}(\text{O})\text{NHR}^{15}$;

$\text{R}^{10\text{A}}$ is selected from H,

- 5 C_{1-6} alkyl substituted with 0-1 $\text{R}^{10\text{B}}$,
 C_{2-6} alkenyl substituted with 0-1 $\text{R}^{10\text{B}}$,
 C_{2-6} alkynyl substituted with 0-1 $\text{R}^{10\text{B}}$, and
 C_{1-6} alkoxy;

10 $\text{R}^{10\text{B}}$ is selected from

- C_{1-4} alkoxy,
 C_{3-6} cycloalkyl,
 C_{3-10} carbocyclic residue substituted with 0-3 R^{33} ,
 phenyl substituted with 0-3 R^{33} , and
 15 5-6 membered heterocyclic ring system containing 1, 2,
 or 3 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-2
 R^{44} ;

20 R^{11} is selected from

- H, halo, $-\text{CF}_3$, $-\text{CN}$, $-\text{NO}_2$,
 C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-4} haloalkyl,
 C_{1-8} alkoxy, C_{3-10} cycloalkyl,
 C_{3-10} carbocyclic residue substituted with 0-3 R^{33} ,
 25 aryl substituted with 0-5 R^{33} ,
 5-10 membered heterocyclic ring system containing from
 1-4 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-3
 R^{31} ;

30

OR^{12} , SR^{12} , $\text{NR}^{12}\text{R}^{13}$, $\text{C}(\text{O})\text{H}$, $\text{C}(\text{O})\text{R}^{12}$, $\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$,
 $\text{NR}^{14}\text{C}(\text{O})\text{R}^{12}$, $\text{C}(\text{O})\text{OR}^{12}$, $\text{OC}(\text{O})\text{R}^{12}$, $\text{OC}(\text{O})\text{OR}^{12}$,
 $\text{CH}(=\text{NR}^{14})\text{NR}^{12}\text{R}^{13}$, $\text{NHC}(=\text{NR}^{14})\text{NR}^{12}\text{R}^{13}$, $\text{S}(\text{O})\text{R}^{12}$, $\text{S}(\text{O})_2\text{R}^{12}$,

$S(O)NR^{12}R^{13}$, $S(O)_2NR^{12}R^{13}$, $NR^{14}S(O)R^{12}$, $NR^{14}S(O)_2R^{12}$,
 $NR^{12}C(O)R^{15}$, $NR^{12}C(O)OR^{15}$, $NR^{12}S(O)_2R^{15}$, and
 $NR^{12}C(O)NHR^{15}$;

5 R^{12} , at each occurrence, is independently selected from
 C_{1-4} alkyl substituted with 0-1 R^{12a} ,
 C_{2-4} alkenyl substituted with 0-1 R^{12a} ,
 C_{2-4} alkynyl substituted with 0-1 R^{12a} ,
 C_{3-6} cycloalkyl substituted with 0-3 R^{33} ,
10 phenyl substituted with 0-5 R^{33} ;
 C_{3-10} carbocyclic residue substituted with 0-3 R^{33} , and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
15 R^{31} ;

R^{12a} , at each occurrence, is independently selected from
phenyl substituted with 0-5 R^{33} ;
 C_{3-10} carbocyclic residue substituted with 0-3 R^{33} , and
20 5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
 R^{31} ;

25 R^{13} , at each occurrence, is independently selected from
H, C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl;

alternatively, R^{12} and R^{13} join to form a 5- or 6-membered
30 ring optionally substituted with -O- or -N(R^{14})-;

alternatively, R^{12} and R^{13} when attached to N may be
combined to form a 9- or 10-membered bicyclic
heterocyclic ring system containing from 1-3

heteroatoms selected from the group consisting of N, O, and S, wherein said bicyclic heterocyclic ring system is unsaturated or partially saturated, wherein said bicyclic heterocyclic ring system is substituted with 0-3 R¹⁶;

R¹⁴, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

R¹⁵, at each occurrence, is independently selected from H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

R¹⁶, at each occurrence, is independently selected from H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₃ haloalkyl-oxy-, and C₁₋₃ alkyloxy-;

R³¹, at each occurrence, is independently selected from H, OH, halo, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, and C₁₋₄ alkyl;

20

R³³, at each occurrence, is independently selected from H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-, C₁₋₄ alkyloxy-, C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-, C₁₋₄ alkyl-OC(=O)-, C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆ cycloalkylmethyl-oxy-;

25

C₁₋₆ alkyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy; and C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy;

30

R⁴¹, at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN;
C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl
C₁₋₄ alkyl substituted with 0-1 R⁴³,
5 aryl substituted with 0-3 R⁴², and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴⁴;

10

R⁴², at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,
CH(=NH)NH₂, NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
15 C₃₋₆ cycloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴⁴, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
20 consisting of N, O, and S substituted with 0-3
R⁴⁴;

R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;

25 R⁴⁴, at each occurrence, is independently selected from H,
halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂,
C₁₋₄ alkyl, and C₁₋₄ alkoxy;

R⁴⁵ is C₁₋₄ alkyl;

30

R⁴⁶, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;

R⁴⁷, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;

k is 1 or 2;

5

m is 0, 1, or 2; and

n is 1, 2, or 3.

10

[4] In a more preferred embodiment of the present
invention,

X is -NR^{10A}-;

15

R¹ is selected from

H,

C(=O)R²,

C(=O)OR²,

20

C₁₋₆ alkyl,

C₂₋₆ alkenyl,

C₂₋₆ alkynyl,

C₃₋₆ cycloalkyl,

C₁₋₄ alkyl substituted with 0-2 R²,

25

C₂₋₄ alkenyl substituted with 0-2 R², and

C₂₋₄ alkynyl substituted with 0-2 R²;

R², at each occurrence, is independently selected from

C₁₋₄ alkyl,

30

C₂₋₄ alkenyl,

C₂₋₄ alkynyl,

C₃₋₆ cycloalkyl,

phenyl substituted with 0-5 R⁴²;

C₃₋₁₀ carbocyclic residue substituted with 0-3 R⁴¹, and

5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴¹;

5

R⁵ is H, methyl, ethyl, propyl, or butyl;

R^{6a} is selected independently from

H, -OH, -NR⁴⁶R⁴⁷, -CF₃, C₁₋₃ alkyl, and C₁₋₃ alkoxy;

10

R^{6b} is H;

R⁷ and R⁹, at each occurrence, are independently selected
from

15 H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,
C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl,
C₁₋₆ alkoxy, (C₁₋₄ haloalkyl)oxy,
C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
C₁₋₄ alkyl substituted with 0-2 R¹¹,

20 C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³,

5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
25 R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,
CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹²,
30 S(O)₂R¹², S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹²,
and NR¹⁴S(O)₂R¹²;

R⁸ is selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂,

- C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl,
C₁₋₆ alkoxy, (C₁₋₄ haloalkyl)oxy,
C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
C₁₋₄ alkyl substituted with 0-2 R¹¹,
5 C₂₋₄ alkenyl substituted with 0-2 R¹¹,
C₂₋₄ alkynyl substituted with 0-1 R¹¹,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³,
5-10 membered heterocyclic ring system containing from
10 1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;
- OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
15 NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,
CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹²,
S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹²,
NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and
NR¹²C(O)NHR¹⁵;
- 20 R^{10A} is selected from H,
C₁₋₄ alkyl substituted with 0-1 R^{10B},
C₂₋₄ alkenyl substituted with 0-1 R^{10B},
C₂₋₄ alkynyl substituted with 0-1 R^{10B}, and
25 C₁₋₆ alkoxy;
- R^{10B} is selected from
C₁₋₄ alkoxy,
C₃₋₆ cycloalkyl,
30 phenyl substituted with 0-3 R³³, and
5-6 membered heterocyclic ring system containing 1, 2,
or 3 heteroatoms selected from the group

consisting of N, O, and S substituted with 0-2
R⁴⁴;

R¹¹ is selected from

- 5 H, halo, -CF₃, -CN, -NO₂, C₁₋₆ alkyl,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy,
C₃₋₁₀ cycloalkyl,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³,
10 5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;

- 15 OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,
CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹²,
S(O)₂R¹², S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹²,
and NR¹⁴S(O)₂R¹²;

20

R¹², at each occurrence, is independently selected from

- C₁₋₄ alkyl substituted with 0-1 R^{12a},
C₂₋₄ alkenyl substituted with 0-1 R^{12a},
C₂₋₄ alkynyl substituted with 0-1 R^{12a},
25 C₃₋₆ cycloalkyl substituted with 0-3 R³³,
phenyl substituted with 0-5 R³³;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
30 consisting of N, O, and S substituted with 0-3
R³¹;

R^{12a}, at each occurrence, is independently selected from

phenyl substituted with 0-5 R^{33} ;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R^{33} , and
5 5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
 R^{31} ;

R^{13} , at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

10 alternatively, R^{12} and R^{13} join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R^{14})-;

alternatively, R^{12} and R^{13} when attached to N may be
15 combined to form a 9- or 10-membered bicyclic
heterocyclic ring system containing from 1-3
heteroatoms selected from the group consisting of N,
O, and S, wherein said bicyclic heterocyclic ring
system is unsaturated or partially saturated, wherein
20 said bicyclic heterocyclic ring system is substituted
with 0-3 R^{16} ;

R^{14} , at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;

25 R^{15} , at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

R^{16} , at each occurrence, is independently selected from
30 H, OH, F, Cl, CN, NO₂, CF₃, SO₂ R^{45} , NR⁴⁶ R^{47} , -C(=O)H,
methyl, ethyl, methoxy, ethoxy, trifluoromethyl, and
trifluoromethoxy;

R^{31} , at each occurrence, is independently selected from

H, OH, halo, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, and C₁₋₄ alkyl;

R³³, at each occurrence, is independently selected from
 H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
 5 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
 C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-,
 C₁₋₄ alkyloxy-,
 C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-,
 C₁₋₄ alkyl-OC(=O)-,
 10 C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆
 cycloalkylmethyl-oxy-;
 C₁₋₆ alkyl substituted with OH, methoxy, ethoxy,
 propoxy, or butoxy; and
 C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy,
 15 propoxy, or butoxy;

R⁴¹, at each occurrence, is independently selected from
 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,
 C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl
 20 C₁₋₄ alkyl substituted with 0-1 R⁴³,
 aryl substituted with 0-3 R⁴², and
 5-10 membered heterocyclic ring system containing from
 1-4 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-3
 25 R⁴⁴;

R⁴², at each occurrence, is independently selected from
 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,
 CH(=NH)NH₂, NHC(=NH)NH₂,
 30 C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
 C₃₋₆ cycloalkyl,
 C₁₋₄ alkyl substituted with 0-1 R⁴³,
 aryl substituted with 0-3 R⁴⁴, and

5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴⁴;

5

R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;

R⁴⁴, at each occurrence, is independently selected from H,
halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂,
10 C₁₋₄ alkyl, and C₁₋₄ alkoxy;

R⁴⁵ is C₁₋₄ alkyl;

R⁴⁶, at each occurrence, is independently selected from H
15 and C₁₋₄ alkyl;

R⁴⁷, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;

20 k is 1 or 2;

m is 0 or 1; and

n is 1 or 2.

25

[5] In an even more preferred embodiment of the
present invention,

X is -NH-;

30

R¹ is selected from
H,
C₁₋₄ alkyl,
C₂₋₄ alkenyl,

C₂₋₄ alkynyl,
C₃₋₄ cycloalkyl,
C₁₋₃ alkyl substituted with 0-1 R²,
C₂₋₃ alkenyl substituted with 0-1 R², and
5 C₂₋₃ alkynyl substituted with 0-1 R²;

R², at each occurrence, is independently selected from
C₁₋₄ alkyl,
C₂₋₄ alkenyl,
10 C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
phenyl substituted with 0-5 R⁴²;
C₃₋₆ carbocyclic residue substituted with 0-3 R⁴¹, and
5-6 membered heterocyclic ring system containing 1, 2,
15 or 3 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴¹;

R⁵ is H, methyl, ethyl, propyl, or butyl;

20

R^{6a} is H, methyl, ethyl, methoxy, -OH, or -CF₃;

R^{6b} is H;

25 R⁷ and R⁹, at each occurrence, are independently selected
from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl,
C₁₋₄ alkoxy, (C₁₋₄ haloalkyl)oxy,
30 C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
C₁₋₄ alkyl substituted with 0-2 R¹¹,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³, and

5-6 membered heterocyclic ring system containing 1, 2,
or 3 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;

5

R⁸ is selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂,

C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl,

C₁₋₄ alkoxy, (C₁₋₄ haloalkyl)oxy,

10 C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,

C₁₋₄ alkyl substituted with 0-2 R¹¹,

C₂₋₄ alkenyl substituted with 0-2 R¹¹,

C₂₋₄ alkynyl substituted with 0-1 R¹¹,

C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,

15 aryl substituted with 0-5 R³³,

5-6 membered heterocyclic ring system containing 1, 2,
or 3 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;

20 OR¹², SR¹², NR¹²R¹³, NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵,
NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;

R¹¹ is selected from

H, halo, -CF₃, -CN, -NO₂,

25 C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl,
C₁₋₄ alkoxy, (C₁₋₄ haloalkyl)oxy,

C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,

C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,

aryl substituted with 0-5 R³³, and

30 5-6 membered heterocyclic ring system containing 1, 2,
or 3 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;

R¹², at each occurrence, is independently selected from
C₁₋₄ alkyl substituted with 0-1 R^{12a},
C₂₋₄ alkenyl substituted with 0-1 R^{12a},
5 C₂₋₄ alkynyl substituted with 0-1 R^{12a},
C₃₋₆ cycloalkyl substituted with 0-3 R³³,
phenyl substituted with 0-5 R³³;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and
5-10 membered heterocyclic ring system containing from
10 1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;

R^{12a}, at each occurrence, is independently selected from
15 phenyl substituted with 0-5 R³³;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
20 R³¹;

R¹³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;
25 alternatively, R¹² and R¹³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R¹⁴)-;

alternatively, R¹² and R¹³ when attached to N may be
combined to form a 9- or 10-membered bicyclic
30 heterocyclic ring system containing from 1-3
heteroatoms selected from the group consisting of one
N, two N, three N, one N one O, and one N one S;
wherein said bicyclic heterocyclic ring system is
unsaturated or partially saturated, wherein said

bicyclic heterocyclic ring system is substituted with
0-2 R¹⁶;

5 R¹⁴, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;

R¹⁵, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;

10 R¹⁶, at each occurrence, is independently selected from
H, OH, F, Cl, CN, NO₂, methyl, ethyl, methoxy, ethoxy,
trifluoromethyl, and trifluoromethoxy;

15 R³¹, at each occurrence, is independently selected from
H, OH, halo, CF₃, methyl, ethyl, and propyl;

R³³, at each occurrence, is independently selected from
H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
20 C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-,
C₁₋₄ alkyloxy-,
C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-,
C₁₋₄ alkyl-OC(=O)-,
C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆
25 cycloalkylmethyl-oxy-;
C₁₋₆ alkyl substituted with OH, methoxy, ethoxy,
propoxy, or butoxy; and
C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy,
propoxy, or butoxy;

30 R⁴¹, at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,
C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl,
and C₁₋₃ alkyl;

R⁴², at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,
CH(=NH)NH₂, NHC(=NH)NH₂,
5 C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl,
C₃₋₆ cycloalkyl, and C₁₋₃ alkyl;

R⁴³ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
phenyl, or pyridyl, each substituted with 0-3 R⁴⁴;
10

R⁴⁴, at each occurrence, is independently selected from H,
halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂,
methyl, ethyl, propyl, butyl, methoxy, ethoxy,
propoxy, and butoxy;

15

R⁴⁵ is methyl, ethyl, propyl, or butyl;

20

R⁴⁶, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;

R⁴⁷, at each occurrence, is independently selected from
from H, methyl, ethyl, propyl, and butyl;

25

k is 1;

m is 1; and

n is 1 or 2.

30 [6] In another even more preferred embodiment of the
present invention,

X is -NH-;

35 R¹ is selected from

- H,
C₁₋₄ alkyl,
C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
5 C₃₋₄ cycloalkyl,
C₁₋₃ alkyl substituted with 0-1 R²,
C₂₋₃ alkenyl substituted with 0-1 R², and
C₂₋₃ alkynyl substituted with 0-1 R²;
- 10 R², at each occurrence, is independently selected from
C₁₋₄ alkyl,
C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
15 phenyl substituted with 0-5 R⁴²;
C₃₋₆ carbocyclic residue substituted with 0-3 R⁴¹, and
5-6 membered heterocyclic ring system containing 1, 2,
or 3 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
20 R⁴¹;
- R⁵ is H, methyl, ethyl, propyl, or butyl;
- R^{6a} is H, methyl, ethyl, methoxy, -OH, or -CF₃;
- 25 R^{6b} is H;
- R⁷ and R⁹, at each occurrence, are independently selected
from
30 H, F, Cl, -CH₃, -OCH₃, -CF₃, -OCF₃, -CN, and -NO₂,
- R⁸ is selected from
H, F, Cl, Br, -CF₃, -OCF₃, -OH, -CN, -NO₂,

C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl,
C₁₋₄ alkoxy, (C₁₋₄ haloalkyl)oxy,
C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
C₁₋₄ alkyl substituted with 0-2 R¹¹,
5 C₂₋₄ alkenyl substituted with 0-2 R¹¹,
C₂₋₄ alkynyl substituted with 0-1 R¹¹,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³,
5-6 membered heterocyclic ring system containing 1, 2,
10 or 3 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;
OR¹², SR¹², NR¹²R¹³, NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵,
NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;

15

R¹¹ is selected from

H, halo, -CF₃, -CN, -NO₂,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl,
C₁₋₄ alkoxy, (C₁₋₄ haloalkyl)oxy,
20 C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³, and
5-6 membered heterocyclic ring system containing 1, 2,
or 3 heteroatoms selected from the group
25 consisting of N, O, and S substituted with 0-3
R³¹;

R¹², at each occurrence, is independently selected from
C₁₋₄ alkyl substituted with 0-1 R^{12a},
30 C₂₋₄ alkenyl substituted with 0-1 R^{12a},
C₂₋₄ alkynyl substituted with 0-1 R^{12a},
C₃₋₆ cycloalkyl substituted with 0-3 R³³,
phenyl substituted with 0-5 R³³;

C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
5 R³¹;

R^{12a}, at each occurrence, is independently selected from
phenyl substituted with 0-5 R³³;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and
10 5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;

15 R¹³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

alternatively, R¹² and R¹³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R¹⁴)-;

20 alternatively, R¹² and R¹³ when attached to N may be
combined to form a 9- or 10-membered bicyclic
heterocyclic ring system containing from 1-3
heteroatoms selected from the group consisting of N,
25 O, and S; wherein said bicyclic heterocyclic ring
system is selected from indolyl, indolinyl, indazolyl,
benzimidazolyl, benzimidazolinyl, benztriazolyl,
benzoxazolyl, benzoxazolinyl, benzthiazolyl, and
dioxobenzthiazolyl; wherein said bicyclic heterocyclic
30 ring system is substituted with 0-1 R¹⁶;

R¹⁴, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;

- R¹⁵, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and butyl;
- 5 R¹⁶, at each occurrence, is independently selected from H, OH, F, Cl, CN, NO₂, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, and trifluoromethoxy;
- R³¹, at each occurrence, is independently selected from H, OH, halo, CF₃, methyl, ethyl, and propyl;
- 10 R³³, at each occurrence, is independently selected from H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-,
- 15 C₁₋₄ alkyloxy-, C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-, C₁₋₄ alkyl-OC(=O)-, C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆ cycloalkylmethyl-oxy-;
- 20 C₁₋₆ alkyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy; and C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy;
- 25 R⁴¹, at each occurrence, is independently selected from H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, and C₁₋₃ alkyl;
- 30 R⁴², at each occurrence, is independently selected from H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, CH(=NH)NH₂, NHC(=NH)NH₂, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl, C₃₋₆ cycloalkyl, and C₁₋₃ alkyl;

R⁴³ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, or pyridyl, each substituted with 0-3 R⁴⁴;

5 R⁴⁴, at each occurrence, is independently selected from H, halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, and butoxy;

10 R⁴⁵ is methyl, ethyl, propyl, or butyl;

R⁴⁶, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and butyl;

15 R⁴⁷, at each occurrence, is independently selected from from H, methyl, ethyl, propyl, and butyl;

k is 1;

20 m is 1; and

n is 1 or 2.

[7] In another even more preferred embodiment of the
25 present invention,

X is -NH-;

R¹ is selected from H,

30 C₁₋₅ alkyl substituted with 0-1 R²,
C₂₋₅ alkenyl substituted with 0-1 R², and
C₂₋₃ alkynyl substituted with 0-1 R²;

R² is C₃₋₆ cycloalkyl;

R⁵ is H, methyl, ethyl, or propyl;

R^{6a} is H, methyl, or ethyl;

5

R^{6b} is H;

R⁷ and R⁹, at each occurrence, are independently selected
from

10 H, F, Cl, -CH₃, -OCH₃, -CF₃, -OCF₃, -CN, and -NO₂,

R⁸ is selected from

methyl substituted with R¹¹;

ethenyl substituted with R¹¹;

15 OR¹², SR¹², NR¹²R¹³, NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵,
NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;

R¹¹ is selected from

phenyl- substituted with 0-5 fluoro;

20 2-(H₃CCH₂C(=O))-phenyl- substituted with R³³;

2-(H₃CC(=O))-phenyl- substituted with R³³;

2-(HC(=O))-phenyl- substituted with R³³;

2-(H₃CCH(OH))-phenyl- substituted with R³³;

2-(H₃CCH₂CH(OH))-phenyl- substituted with R³³;

25 2-(HOCH₂)-phenyl- substituted with R³³;

2-(HOCH₂CH₂)-phenyl- substituted with R³³;

2-(H₃COCH₂)-phenyl- substituted with R³³;

2-(H₃COCH₂CH₂)-phenyl- substituted with R³³;

2-(H₃CCH(OMe))-phenyl- substituted with R³³;

30 2-(H₃COC(=O))-phenyl- substituted with R³³;

2-(HOCH₂CH=CH)-phenyl- substituted with R³³;

2-((MeOC(=O)CH=CH)-phenyl- substituted with R³³;

2-(methyl)-phenyl- substituted with R³³;

- 2-(ethyl)-phenyl- substituted with R^{33} ;
2-(i-propyl)-phenyl- substituted with R^{33} ;
2-(F₃C)-phenyl- substituted with R^{33} ;
2-(NC)-phenyl- substituted with R^{33} ;
5 2-(H₃CO)-phenyl- substituted with R^{33} ;
2-(fluoro)-phenyl- substituted with R^{33} ;
2-(chloro)-phenyl- substituted with R^{33} ;
3-(NC)-phenyl- substituted with R^{33} ;
3-(H₃CO)-phenyl- substituted with R^{33} ;
10 3-(fluoro)-phenyl- substituted with R^{33} ;
3-(chloro)-phenyl- substituted with R^{33} ;
4-(NC)-phenyl- substituted with R^{33} ;
4-(fluoro)-phenyl- substituted with R^{33} ;
4-(chloro)-phenyl- substituted with R^{33} ;
15 4-(H₃CS)-phenyl- substituted with R^{33} ;
4-(H₃CO)-phenyl- substituted with R^{33} ;
4-(ethoxy)-phenyl- substituted with R^{33} ;
4-(i-propoxy)-phenyl- substituted with R^{33} ;
4-(i-butoxy)-phenyl- substituted with R^{33} ;
20 4-(H₃CCH₂CH₂C(=O))-phenyl- substituted with R^{33} ;
4-((H₃C)₂CHC(=O))-phenyl- substituted with R^{33} ;
4-(H₃CCH₂C(=O))-phenyl- substituted with R^{33} ;
4-(H₃CC(=O))-phenyl- substituted with R^{33} ;
4-(H₃CCH₂CH₂CH(OH))-phenyl- substituted with R^{33} ;
25 4-((H₃C)₂CHCH(OH))-phenyl- substituted with R^{33} ;
4-(H₃CCH₂CH(OH))-phenyl- substituted with R^{33} ;
4-(H₃CCH(OH))-phenyl- substituted with R^{33} ;
4-(cyclopropyloxy)-phenyl- substituted with R^{33} ;
4-(cyclobutyloxy)-phenyl- substituted with R^{33} ; and
30 4-(cyclopentyloxy)-phenyl- substituted with R^{33} ;

R^{12} is selected from

- phenyl- substituted with 0-5 fluoro;
2-(H₃CCH₂C(=O))-phenyl- substituted with R³³;
2-(H₃CC(=O))-phenyl- substituted with R³³;
2-(HC(=O))-phenyl- substituted with R³³;
5 2-(H₃CCH(OH))-phenyl- substituted with R³³;
2-(H₃CCH₂CH(OH))-phenyl- substituted with R³³;
2-(HOCH₂)-phenyl- substituted with R³³;
2-(HOCH₂CH₂)-phenyl- substituted with R³³;
2-(H₃COCH₂)-phenyl- substituted with R³³;
10 2-(H₃COCH₂CH₂)-phenyl- substituted with R³³;
2-(H₃CCH(OMe))-phenyl- substituted with R³³;
2-(H₃COC(=O))-phenyl- substituted with R³³;
2-(HOCH₂CH=CH)-phenyl- substituted with R³³;
2-((MeOC=O)CH=CH)-phenyl- substituted with R³³;
15 2-(methyl)-phenyl- substituted with R³³;
2-(ethyl)-phenyl- substituted with R³³;
2-(i-propyl)-phenyl- substituted with R³³;
2-(F₃C)-phenyl- substituted with R³³;
2-(NC)-phenyl- substituted with R³³;
20 2-(H₃CO)-phenyl- substituted with R³³;
2-(fluoro)-phenyl- substituted with R³³;
2-(chloro)-phenyl- substituted with R³³;
3-(NC)-phenyl- substituted with R³³;
3-(H₃CO)-phenyl- substituted with R³³;
25 3-(fluoro)-phenyl- substituted with R³³;
3-(chloro)-phenyl- substituted with R³³;
4-(NC)-phenyl- substituted with R³³;
4-(fluoro)-phenyl- substituted with R³³;
4-(chloro)-phenyl- substituted with R³³;
30 4-(H₃CS)-phenyl- substituted with R³³;
4-(H₃CO)-phenyl- substituted with R³³;
4-(ethoxy)-phenyl- substituted with R³³;

4-(i-propoxy)-phenyl- substituted with R^{33} ;
4-(i-butoxy)-phenyl- substituted with R^{33} ;
4-($H_3CCH_2CH_2C(=O)$)-phenyl- substituted with R^{33} ;
4-($(H_3C)_2CHC(=O)$)-phenyl- substituted with R^{33} ;
5 4-($H_3CCH_2C(=O)$)-phenyl- substituted with R^{33} ;
4-($H_3CC(=O)$)-phenyl- substituted with R^{33} ;
4-($H_3CCH_2CH_2CH(OH)$)-phenyl- substituted with R^{33} ;
4-($(H_3C)_2CHCH(OH)$)-phenyl- substituted with R^{33} ;
4-($H_3CCH_2CH(OH)$)-phenyl- substituted with R^{33} ;
10 4-($H_3CCH(OH)$)-phenyl- substituted with R^{33} ;
4-(cyclopropyloxy)-phenyl- substituted with R^{33} ;
4-(cyclobutyloxy)-phenyl- substituted with R^{33} ; and
4-(cyclopentyloxy)-phenyl- substituted with R^{33} ;

15 R^{13} is H, methyl, or ethyl;

alternatively, R^{12} and R^{13} join to form a 5- or 6-membered
ring selected from pyrrolyl, pyrrolidinyl, imidazolyl,
piperidinyl, piperizinyll, methylpiperizinyll, and
20 morpholinyl;

alternatively, R^{12} and R^{13} when attached to N may be
combined to form a 9- or 10-membered bicyclic
heterocyclic ring system containing from 1-3
25 heteroatoms selected from the group consisting of N,
O, and S; wherein said bicyclic heterocyclic ring
system is selected from indolyl, indolinyl, indazolyl,
benzimidazolyl, benzimidazolinyl, benztriazolyl,
benzoxazolyl, benzoxazolinyl, benzthiazolyl, and
30 dioxobenzthiazolyl; wherein said bicyclic heterocyclic
ring system is substituted with 0-1 R^{16} ;

R^{15} is H, methyl, ethyl, propyl, or butyl;

R¹⁶, at each occurrence, is independently selected from
H, OH, F, Cl, CN, NO₂, methyl, ethyl, methoxy, ethoxy,
trifluoromethyl, and trifluoromethoxy;

5

R³³, at each occurrence, is independently selected from
H, F, Cl, -CH₃, -OCH₃, -CF₃, -OCF₃, -CN, and -NO₂;

k is 1;

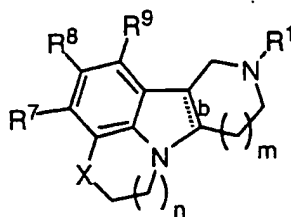
10

m is 1; and

n is 1 or 2.

15

[8] In an even more preferred embodiment of the
present invention, the compound of Formula (I) is selected
from Formula (I-a):



20

(I-a)

wherein:

25 b is a single bond or a double bond;

X is -NR^{10A}-;

R¹ is selected from

30 hydrogen, methyl, ethyl, n-propyl, n-butyl, s-butyl,

t-butyl, n-pentyl, n-hexyl, 2-propyl, 2-butyl, 2-pentyl,
2-hexyl, 2-methylpropyl, 2-methylbutyl, 2-methylpentyl,
2-ethylbutyl, 3-methylpentyl, 3-methylbutyl,
4-methylpentyl, 2-fluoroethyl, 2,2-difluoroethyl,
5 2,2,2-trifluoroethyl,

2-propenyl, 2-methyl-2-propenyl, trans-2-butenyl,
3-methyl-butenyl, 3-butenyl, trans-2-pentenyl,
cis-2-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl,
10 3,3-dichloro-2-propenyl, trans-3-phenyl-2-propenyl,

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl,
cyclohexylmethyl,

15 benzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl,
2,5-dimethylbenzyl, 2,4-dimethylbenzyl, 3,5-
dimethylbenzyl,
2,4,6-trimethyl-benzyl, 3-methoxy-benzyl, 3,5-dimethoxy-
20 benzyl, pentafluorobenzyl, 2-phenylethyl, 1-phenyl-2-
propyl, 4-phenylbutyl, 4-phenylbenzyl, 2-phenylbenzyl,

(2,3-dimethoxy-phenyl)C(=O)-, (2,5-dimethoxy-
phenyl)C(=O)-, (3,4-dimethoxy-phenyl)C(=O)-,
25 (3,5-dimethoxy-phenyl)C(=O)-, cyclopropyl-C(=O)-,
isopropyl-C(=O)-, ethyl-CO₂-, propyl-CO₂-, t-butyl-CO₂-,
2,6-dimethoxy-benzyl, 2,4-dimethoxy-benzyl,
2,4,6-trimethoxy-benzyl, 2,3-dimethoxy-benzyl,
2,4,5-trimethoxy-benzyl, 2,3,4-trimethoxy-benzyl,
30 3,4-dimethoxy-benzyl, 3,4,5-trimethoxy-benzyl,
(4-fluoro-phenyl)ethyl,

-CH=CH₂, -CH₂-CH=CH₂, -CH=CH-CH₃, -C≡CH, -C≡C-CH₃, and
-CH₂-C≡CH;

35

R⁷, R⁸, and R⁹, at each occurrence, are independently
selected from
hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl,
propyl, isopropyl, butyl, t-butyl, nitro,
5 trifluoromethyl, methoxy, ethoxy, isopropoxy,
trifluoromethoxy, phenyl,

methylC(=O)-, ethylC(=O)-, propylC(=O)-, isopropylC(=O)-,
butylC(=O)-, phenylC(=O)-,
10 methylCO₂-, ethylCO₂-, propylCO₂-, isopropylCO₂-,
butylCO₂-, phenylCO₂-,

dimethylamino-S(=O)-, diethylamino-S(=O)-,
15 dipropylamino-S(=O)-, di-isopropylamino-S(=O)-,
dibutylamino-S(=O)-, diphenylamino-S(=O)-,

dimethylamino-SO₂-, diethylamino-SO₂-, dipropylamino-SO₂-
, di-isopropylamino-SO₂-, dibutylamino-SO₂-,
20 diphenylamino-SO₂-,

dimethylamino-C(=O)-, diethylamino-C(=O)-,
dipropylamino-C(=O)-, di-isopropylamino-C(=O)-,
dibutylamino-C(=O)-, diphenylamino-C(=O)-,
25 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-
cyanophenyl, 2-methylphenyl, 2-trifluoromethylphenyl,
2-methoxyphenyl, 2-trifluoromethoxyphenyl,

30 3-chlorophenyl, 3-fluorophenyl, 3-bromophenyl,
3-cyanophenyl, 3-methylphenyl, 3-ethylphenyl,
3-propylphenyl, 3-isopropylphenyl, 3-butylphenyl,
3-trifluoromethylphenyl, 3-methoxyphenyl,
3-isopropoxyphenyl, 3-trifluoromethoxyphenyl,
35 3-thiomethoxyphenyl,

- 4-chlorophenyl, 4-fluorophenyl, 4-bromophenyl,
4-cyanophenyl, 4-methylphenyl, 4-ethylphenyl,
4-propylphenyl, 4-isopropylphenyl, 4-butylphenyl,
5 4-trifluoromethylphenyl, 4-methoxyphenyl,
4-isopropoxyphenyl, 4-trifluoromethoxyphenyl,
4-thiomethoxyphenyl,
- 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,3-
10 dimethylphenyl,
2,3-ditrifluoromethylphenyl, 2,3-dimethoxyphenyl,
2,3-ditrifluoromethoxyphenyl,
- 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,4-
15 dimethylphenyl,
2,4-ditrifluoromethylphenyl, 2,4-dimethoxyphenyl,
2,4-ditrifluoromethoxyphenyl,
- 2,5-dichlorophenyl, 2,5-difluorophenyl, 2,5-
20 dimethylphenyl,
2,5-ditrifluoromethylphenyl, 2,5-dimethoxyphenyl,
2,5-ditrifluoromethoxyphenyl,
- 2,6-dichlorophenyl, 2,6-difluorophenyl, 2,6-
25 dimethylphenyl,
2,6-ditrifluoromethylphenyl, 2,6-dimethoxyphenyl,
2,6-ditrifluoromethoxyphenyl,
- 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-
30 dimethylphenyl,
3,4-ditrifluoromethylphenyl, 3,4-dimethoxyphenyl,
3,4-ditrifluoromethoxyphenyl,
- 2,4,6-trichlorophenyl, 2,4,6-trifluorophenyl,
35 2,4,6-trimethylphenyl, 2,4,6-tritrifluoromethylphenyl,
2,4,6-trimethoxyphenyl, 2,4,6-tritrifluoromethoxyphenyl,

- 2-chloro-4-CF₃-phenyl, 2-fluoro-3-chloro-phenyl,
 2-chloro-4-CF₃-phenyl, 2-chloro-4-methoxy-phenyl,
 2-methoxy-4-isopropyl-phenyl, 2-CF₃-4-methoxy-phenyl,
 5 2-methyl-4-methoxy-5-fluoro-phenyl,
 2-methyl-4-methoxy-phenyl, 2-chloro-4-CF₃O-phenyl,
 2,4,5-trimethyl-phenyl, 2-methyl-4-chloro-phenyl,
- methyl-C(=O)NH-, ethyl-C(=O)NH-, propyl-C(=O)NH-,
 10 isopropyl-C(=O)NH-, butyl-C(=O)NH-, phenyl-C(=O)NH-,
- 4-acetylphenyl, 3-acetamidophenyl, 4-pyridyl, 2-furanyl,
 2-thiophenyl, 2-naphthyl;
- 15 2-Me-5-F-phenyl, 2-F-5-Me-phenyl, 2-MeO-5-F-phenyl,
 2-Me-3-Cl-phenyl, 3-NO₂-phenyl, 2-NO₂-phenyl,
 2-Cl-3-Me-phenyl, 2-Me-4-EtO-phenyl, 2-Me-4-F-phenyl,
 2-Cl-6-F-phenyl, 2-Cl-4-(CHF₂)O-phenyl,
 2,4-diMeO-6-F-phenyl, 2-CF₃-6-F-phenyl,
 20 2-MeS-phenyl, 2,6-diCl-4-MeO-phenyl,
 2,3,4-triF-phenyl, 2,6-diF-4-Cl-phenyl,
 2,3,4,6-tetraF-phenyl, 2,3,4,5,6-pentaF-phenyl,
 2-CF₃-4-EtO-phenyl, 2-CF₃-4-iPrO-phenyl,
 2-CF₃-4-Cl-phenyl, 2-CF₃-4-F-phenyl, 2-Cl-4-EtO-phenyl,
 25 2-Cl-4-iPrO-phenyl, 2-Et-4-MeO-phenyl,
 2-CHO-4-MeO-phenyl, 2-CH(OH)Me-4-MeO-phenyl,
 2-CH(OMe)Me-4-MeO-phenyl, 2-C(=O)Me-4-MeO-phenyl,
 2-CH₂(OH)-4-MeO-phenyl, 2-CH₂(OMe)-4-MeO-phenyl,
 2-CH(OH)Et-4-MeO-phenyl, 2-C(=O)Et-4-MeO-phenyl,
 30 (Z)-2-CH=CHCO₂Me-4-MeO-phenyl,
 2-CH₂CH₂CO₂Me-4-MeO-phenyl,
 (Z)-2-CH=CHCH₂(OH)-4-MeO-phenyl,
 (E)-2-CH=CHCO₂Me-4-MeO-phenyl,
 (E)-2-CH=CHCH₂(OH)-4-MeO-phenyl,

- 2-CH₂CH₂OMe-4-MeO-phenyl,
2-F-4-MeO-phenyl, 2-Cl-4-F-phenyl,
(2-Cl-phenyl)-CH=CH-, (3-Cl-phenyl)-CH=CH-,
(2,6-diF-phenyl)-CH=CH-, -CH₂CH=CH₂,
5 phenyl-CH=CH-, (2-Me-4-MeO-phenyl)-CH=CH-,
cyclohexyl, cyclopentyl, cyclohexylmethyl,
-CH₂CH₂CO₂Et, -(CH₂)₃CO₂Et, -(CH₂)₄CO₂Et,
benzyl, 2-F-benzyl, 3-F-benzyl, 4-F-benzyl,
3-MeO-benzyl, 3-OH-benzyl, 2-MeO-benzyl,
10 2-OH-benzyl, 2-CO₂Me-3-MeO-phenyl,
2-Me-4-CN-phenyl, 2-Me-3-CN-phenyl, 2-CF₃-4-CN-phenyl,
3-CHO-phenyl, 3-CH₂(OH)-phenyl, 3-CH₂(OMe)-phenyl,
3-CH₂(NMe₂)-phenyl, 3-CN-4-F-phenyl,
3-CONH₂-4-F-phenyl, 2-CH₂(NH₂)-4-MeO-phenyl-,
15 phenyl-NH-, (4-F-phenyl)-NH-, (2,4-diCl-phenyl)-NH-,
phenyl-C(=O)NH-, benzyl-NH-, (2-Me-4-MeO-phenyl)-NH-,
(2-F-4-MeO-phenyl)-NH-, (2-Me-4-F-phenyl)-NH-,
phenyl-S-, -NMe₂, 1-pyrrolidinyl, and
-N(tosylate)₂,

20

provided that two of R⁷, R⁸, and R⁹, are independently
selected from hydrogen, fluoro, chloro, bromo, cyano,
methyl, ethyl, propyl, isopropyl, butyl, t-butyl, nitro,
trifluoromethyl, methoxy, ethoxy, isopropoxy, and

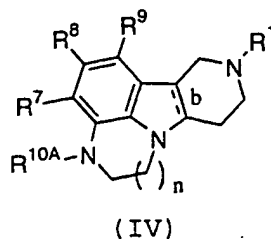
25 trifluoromethoxy;

R^{10A} is selected from hydrogen, methyl, ethyl, benzyl and 4-
fluorobenzyl;

30 m is 1; and

n is 1 or 2.

[9] In an even more preferred embodiment of the present invention, the compound of Formula (I) is selected from Formula (IV):



wherein:

10

b is a single bond, wherein the bridge hydrogens are in a cis position;

R¹ is selected from

15 hydrogen, methyl, ethyl, n-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl, 2-propyl, 2-butyl, 2-pentyl, 2-hexyl, 2-methylpropyl, 2-methylbutyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, 3-methylbutyl, 4-methylpentyl, 2-fluoroethyl, 2,2-difluoroethyl, 20 2,2,2-trifluoroethyl, 2-propenyl, 2-methyl-2-propenyl, trans-2-butenyl, 3-methyl-butenyl, 3-butenyl, trans-2-pentenyl, cis-2-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 3,3-dichloro-2-propenyl, trans-3-phenyl-2-propenyl, cyclopropyl, cyclobutyl, 25 cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, -CH=CH₂, -CH₂-CH=CH₂, -CH=CH-CH₃, -C≡CH, -C≡C-CH₃, and -CH₂-C≡CH;

30 R⁷ and R⁹, at each occurrence, are independently selected from hydrogen, fluoro, methyl, trifluoromethyl, and methoxy;

R⁸ is selected from

hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl,
propyl, isopropyl, butyl, t-butyl, nitro,
5 trifluoromethyl, methoxy, ethoxy, isopropoxy,
trifluoromethoxy, phenyl,

methylC(=O)-, ethylC(=O)-, propylC(=O)-, isopropylC(=O)-,
butylC(=O)-, phenylC(=O)-,

10

methylCO₂-, ethylCO₂-, propylCO₂-, isopropylCO₂-,
butylCO₂-, phenylCO₂-,

dimethylamino-S(=O)-, diethylamino-S(=O)-,
15 dipropylamino-S(=O)-, di-isopropylamino-S(=O)-,
dibutylamino-S(=O)-, diphenylamino-S(=O)-,

dimethylamino-SO₂-, diethylamino-SO₂-, dipropylamino-SO₂-
, di-isopropylamino-SO₂-, dibutylamino-SO₂-,
20 diphenylamino-SO₂-,

dimethylamino-C(=O)-, diethylamino-C(=O)-,
dipropylamino-C(=O)-, di-isopropylamino-C(=O)-,
dibutylamino-C(=O)-, diphenylamino-C(=O)-,

25

2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-
cyanophenyl, 2-methylphenyl, 2-trifluoromethylphenyl,
2-methoxyphenyl, 2-trifluoromethoxyphenyl,

30

3-chlorophenyl, 3-fluorophenyl, 3-bromophenyl,
3-cyanophenyl, 3-methylphenyl, 3-ethylphenyl,
3-propylphenyl, 3-isopropylphenyl, 3-butylphenyl,
3-trifluoromethylphenyl, 3-methoxyphenyl,
3-isopropoxyphenyl, 3-trifluoromethoxyphenyl,

35

3-thiomethoxyphenyl,

- 4-chlorophenyl, 4-fluorophenyl, 4-bromophenyl,
4-cyanophenyl, 4-methylphenyl, 4-ethylphenyl,
4-propylphenyl, 4-isopropylphenyl, 4-butylphenyl,
5 4-trifluoromethylphenyl, 4-methoxyphenyl,
4-isopropoxyphenyl, 4-trifluoromethoxyphenyl,
4-thiomethoxyphenyl,
- 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,3-
10 dimethylphenyl,
2,3-ditrifluoromethylphenyl, 2,3-dimethoxyphenyl,
2,3-ditrifluoromethoxyphenyl,
- 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,4-
15 dimethylphenyl,
2,4-ditrifluoromethylphenyl, 2,4-dimethoxyphenyl,
2,4-ditrifluoromethoxyphenyl,
- 2,5-dichlorophenyl, 2,5-difluorophenyl, 2,5-
20 dimethylphenyl,
2,5-ditrifluoromethylphenyl, 2,5-dimethoxyphenyl,
2,5-ditrifluoromethoxyphenyl,
- 2,6-dichlorophenyl, 2,6-difluorophenyl, 2,6-
25 dimethylphenyl,
2,6-ditrifluoromethylphenyl, 2,6-dimethoxyphenyl,
2,6-ditrifluoromethoxyphenyl,
- 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-
30 dimethylphenyl,
3,4-ditrifluoromethylphenyl, 3,4-dimethoxyphenyl,
3,4-ditrifluoromethoxyphenyl,
- 2,4,6-trichlorophenyl, 2,4,6-trifluorophenyl,
35 2,4,6-trimethylphenyl, 2,4,6-tritrifluoromethylphenyl,
2,4,6-trimethoxyphenyl, 2,4,6-tritrifluoromethoxyphenyl,

- 2-chloro-4-CF₃-phenyl, 2-fluoro-3-chloro-phenyl,
2-chloro-4-CF₃-phenyl, 2-chloro-4-methoxy-phenyl,
2-methoxy-4-isopropyl-phenyl, 2-CF₃-4-methoxy-phenyl,
5 2-methyl-4-methoxy-5-fluoro-phenyl,
2-methyl-4-methoxy-phenyl, 2-chloro-4-CF₃O-phenyl,
2,4,5-trimethyl-phenyl, 2-methyl-4-chloro-phenyl,

methyl-C(=O)NH-, ethyl-C(=O)NH-, propyl-C(=O)NH-,
10 isopropyl-C(=O)NH-, butyl-C(=O)NH-, phenyl-C(=O)NH-,

4-acetylphenyl, 3-acetamidophenyl, 4-pyridyl, 2-furanyl,
2-thiophenyl, 2-naphthyl;

15 2-Me-5-F-phenyl, 2-F-5-Me-phenyl, 2-MeO-5-F-phenyl,
2-Me-3-Cl-phenyl, 3-NO₂-phenyl, 2-NO₂-phenyl,
2-Cl-3-Me-phenyl, 2-Me-4-EtO-phenyl, 2-Me-4-F-phenyl,
2-Cl-6-F-phenyl, 2-Cl-4-(CHF₂)O-phenyl,
2,4-diMeO-6-F-phenyl, 2-CF₃-6-F-phenyl,
20 2-MeS-phenyl, 2,6-diCl-4-MeO-phenyl,
2,3,4-triF-phenyl, 2,6-diF-4-Cl-phenyl,
2,3,4,6-tetraF-phenyl, 2,3,4,5,6-pentaF-phenyl,
2-CF₃-4-EtO-phenyl, 2-CF₃-4-iPrO-phenyl,
2-CF₃-4-Cl-phenyl, 2-CF₃-4-F-phenyl, 2-Cl-4-EtO-phenyl,
25 2-Cl-4-iPrO-phenyl, 2-Et-4-MeO-phenyl,
2-CHO-4-MeO-phenyl, 2-CH(OH)Me-4-MeO-phenyl,
2-CH(OMe)Me-4-MeO-phenyl, 2-C(=O)Me-4-MeO-phenyl,
2-CH₂(OH)-4-MeO-phenyl, 2-CH₂(OMe)-4-MeO-phenyl,
2-CH(OH)Et-4-MeO-phenyl, 2-C(=O)Et-4-MeO-phenyl,
30 (Z)-2-CH=CHCO₂Me-4-MeO-phenyl,
2-CH₂CH₂CO₂Me-4-MeO-phenyl,
(Z)-2-CH=CHCH₂(OH)-4-MeO-phenyl,
(E)-2-CH=CHCO₂Me-4-MeO-phenyl,
(E)-2-CH=CHCH₂(OH)-4-MeO-phenyl,

2-CH₂CH₂OMe-4-MeO-phenyl,
 2-F-4-MeO-phenyl, 2-Cl-4-F-phenyl,
 (2-Cl-phenyl)-CH=CH-, (3-Cl-phenyl)-CH=CH-,
 (2,6-diF-phenyl)-CH=CH-, -CH₂CH=CH₂,
 5 phenyl-CH=CH-, (2-Me-4-MeO-phenyl)-CH=CH-,
 cyclohexyl, cyclopentyl, cyclohexylmethyl,
 -CH₂CH₂CO₂Et, -(CH₂)₃CO₂Et, -(CH₂)₄CO₂Et,
 benzyl, 2-F-benzyl, 3-F-benzyl, 4-F-benzyl,
 3-MeO-benzyl, 3-OH-benzyl, 2-MeO-benzyl,
 10 2-OH-benzyl, 2-CO₂Me-3-MeO-phenyl,
 2-Me-4-CN-phenyl, 2-Me-3-CN-phenyl, 2-CF₃-4-CN-phenyl,
 3-CHO-phenyl, 3-CH₂(OH)-phenyl, 3-CH₂(OMe)-phenyl,
 3-CH₂(NMe₂)-phenyl, 3-CN-4-F-phenyl,
 3-CONH₂-4-F-phenyl, 2-CH₂(NH₂)-4-MeO-phenyl-,
 15 phenyl-NH-, (4-F-phenyl)-NH-, (2,4-diCl-phenyl)-NH-,
 phenyl-C(=O)NH-, benzyl-NH-, (2-Me-4-MeO-phenyl)-NH-,
 (2-F-4-MeO-phenyl)-NH-, (2-Me-4-F-phenyl)-NH-,
 phenyl-S-, -NMe₂, 1-pyrrolidinyl, and
 -N(tosylate)₂;

20

R^{10A} is selected from hydrogen, methyl, ethyl, 4-
 fluorobenzyl and benzyl; and

n is 1 or 2.

25

[10] In another preferred embodiment of the present
 invention,

X is -NR^{10A}-, -C(=O)NR^{10A}-, or -NR^{10A}C(=O)-;

30

R¹ is selected from

C₁₋₆ alkyl substituted with Z,
 C₂₋₆ alkenyl substituted with Z,
 C₂₋₆ alkynyl substituted with Z,

- C₃₋₆ cycloalkyl substituted with Z,
aryl substituted with Z,
5-6 membered heterocyclic ring system containing at
least one heteroatom selected from the group
5 consisting of N, O, and S, said heterocyclic ring
system substituted with Z;
C₁₋₆ alkyl substituted with 0-2 R²,
C₂₋₆ alkenyl substituted with 0-2 R²,
C₂₋₆ alkynyl substituted with 0-2 R²,
10 aryl substituted with 0-2 R², and
5-6 membered heterocyclic ring system containing at
least one heteroatom selected from the group
consisting of N, O, and S, said heterocyclic ring
system substituted with 0-2 R²;
15 Z is selected from H,
-CH(OH)R²,
-C(ethylenedioxy)R²,
-OR²,
20 -SR²,
-NR²R³,
-C(O)R²,
-C(O)NR²R³,
-NR³C(O)R²,
25 -C(O)OR²,
-OC(O)R²,
-CH(=NR⁴)NR²R³,
-NHC(=NR⁴)NR²R³,
-S(O)R²,
30 -S(O)₂R²,
-S(O)₂NR²R³, and -NR³S(O)₂R²;

R², at each occurrence, is independently selected from
C₁₋₄ alkyl,

- C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
aryl substituted with 0-5 R⁴²;
5 C₃₋₁₀ carbocyclic residue substituted with 0-3 R⁴¹, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴¹;
10 R³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, and
C₁₋₄ alkoxy;
15 alternatively, R² and R³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R⁴)-;
R⁴, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;
20 R⁵ is H, methyl, ethyl, propyl, or butyl;
R^{6a} is selected from
H, -OH, -NR⁴⁶R⁴⁷, -CF₃,
25 C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, C₁₋₄
haloalkyl, C₃₋₆ cycloalkyl, and
aryl substituted with 0-3 R⁴⁴;
R^{6b} is H;
30 R⁷, R⁸, and R⁹, at each occurrence, are independently
selected from
H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,

C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl,
C₁₋₈ alkoxy, (C₁₋₄ haloalkyl)oxy,
C₁₋₄ alkyl substituted with 0-2 R¹¹,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
5 aryl substituted with 0-5 R³³,
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;
10
OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,
CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹²,
S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹²,
15 NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and
NR¹²C(O)NHR¹⁵;

R^{10A} is selected from H,
C₁₋₆ alkyl substituted with 0-1 R^{10B},
20 C₂₋₆ alkenyl substituted with 0-1 R^{10B},
C₂₋₆ alkynyl substituted with 0-1 R^{10B}, and
C₁₋₆ alkoxy;

R^{10B} is selected from
25 C₁₋₄ alkoxy,
C₃₋₆ cycloalkyl,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
phenyl substituted with 0-3 R³³, and
5-6 membered heterocyclic ring system containing 1, 2,
30 or 3 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-2
R⁴⁴;

R¹¹ is selected from
H, halo, -CF₃, -CN, -NO₂,
C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl,
C₁₋₈ alkoxy, C₃₋₁₀ cycloalkyl,
5 C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³,
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
10 R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,
CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹²,
15 S(O)₂R¹², S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹²,
and NR¹⁴S(O)₂R¹²;

R¹², at each occurrence, is independently selected from
C₁₋₄ alkyl,
20 C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
phenyl substituted with 0-5 R³³;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and
25 5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;

30 R¹³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

alternatively, R¹² and R¹³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R¹⁴)-;

R¹⁴, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

5 R³¹, at each occurrence, is independently selected from H, OH, halo, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, methyl, ethyl, and propyl;

10 R³³, at each occurrence, is independently selected from H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₃₋₅ cycloalkyl, C₁₋₃ haloalkyl, C₁₋₃ haloalkyl-oxy-, C₁₋₃ alkyloxy-, C₁₋₃ alkylthio-, C₁₋₃ alkyl-C(=O)-, and C₁₋₃ alkyl-C(=O)NH-;

15

R⁴¹, at each occurrence, is independently selected from H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, =O, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ alkyl substituted with 0-1 R⁴³, aryl substituted with 0-3 R⁴², and 20 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-3 R⁴⁴;

25

R⁴², at each occurrence, is independently selected from H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, SR⁴⁵, NR⁴⁶R⁴⁷, OR⁴⁸, NO₂, CN, CH(=NH)NH₂, NHC(=NH)NH₂, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, 30 C₃₋₆ cycloalkyl, C₁₋₄ alkyl substituted with 0-1 R⁴³, aryl substituted with 0-3 R⁴⁴, and 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms selected from the group

consisting of N, O, and S substituted with 0-3
R⁴⁴;

R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;

5

R⁴⁴, at each occurrence, is independently selected from H,
halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂,
C₁₋₄ alkyl, and C₁₋₄ alkoxy;

10 R⁴⁵ is C₁₋₄ alkyl;

R⁴⁶, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;

15 R⁴⁷, at each occurrence, is independently selected from H,
C₁₋₄ alkyl, -C(=O)NH(C₁₋₄ alkyl), -SO₂(C₁₋₄ alkyl),
-SO₂(phenyl), -C(=O)O(C₁₋₄ alkyl), -C(=O)(C₁₋₄ alkyl),
and -C(=O)H;

20 R⁴⁸, at each occurrence, is independently selected from H,
C₁₋₄ alkyl, -C(=O)NH(C₁₋₄ alkyl), -C(=O)O(C₁₋₄ alkyl),
-C(=O)(C₁₋₄ alkyl), and -C(=O)H;

k is 1 or 2;

25

m is 0, 1, or 2; and

n is 1 or 2.

30 [11] In a further preferred embodiment of the present
invention,

X is -NR^{10A}-;

- R^1 is selected from
- C₂₋₅ alkyl substituted with Z,
 - C₂₋₅ alkenyl substituted with Z,
 - C₂₋₅ alkynyl substituted with Z,
 - 5 C₃₋₆ cycloalkyl substituted with Z,
 - aryl substituted with Z,
 - 5-6 membered heterocyclic ring system containing at least one heteroatom selected from the group consisting of N, O, and S, said heterocyclic ring system substituted with Z;
 - 10 C₁₋₅ alkyl substituted with 0-2 R^2 ,
 - C₂₋₅ alkenyl substituted with 0-2 R^2 , and
 - C₂₋₅ alkynyl substituted with 0-2 R^2 ;
- 15 Z is selected from H,
- CH(OH) R^2 ,
 - C(ethylenedioxy) R^2 ,
 - OR²,
 - SR²,
 - 20 -NR²R³,
 - C(O) R^2 ,
 - C(O)NR²R³,
 - NR³C(O) R^2 ,
 - C(O)OR²,
 - 25 -OC(O) R^2 ,
 - CH(=NR⁴)NR²R³,
 - NHC(=NR⁴)NR²R³,
 - S(O) R^2 ,
 - S(O)₂ R^2 ,
 - 30 -S(O)₂NR²R³, and -NR³S(O)₂ R^2 ;

R^2 , at each occurrence, is independently selected from
C₁₋₄ alkyl,

- C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
aryl substituted with 0-5 R⁴²;
- 5 C₃₋₁₀ carbocyclic residue substituted with 0-3 R⁴¹, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴¹;
- 10 R³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, and
C₁₋₄ alkoxy;
- 15 alternatively, R² and R³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R⁴)-;
- R⁴, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;
- 20 R⁵ is H, methyl, or ethyl;
- R^{6a} is selected from
H, -OH, -NR⁴⁶R⁴⁷, -CF₃,
25 C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, C₁₋₄
haloalkyl, and C₃₋₆ cycloalkyl;
- R^{6b} is H;
- 30 R⁷, R⁸, and R⁹, at each occurrence, are independently
selected from
H, halo, -CF₃, -OCF₃, -OH, -OCH₃, -CN, -NO₂, -NR⁴⁶R⁴⁷,
C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl,
C₁₋₆ alkoxy, (C₁₋₄ haloalkyl)oxy,

- C₁₋₄ alkyl substituted with 0-2 R¹¹,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³,
5 5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;
- OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
10 NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², CH(=NR¹⁴)NR¹²R¹³,
NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)₂NR¹²R¹³,
NR¹⁴S(O)₂R¹², NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵,
NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;
- 15 R^{10A} is selected from H,
C₁₋₆ alkyl substituted with 0-1 R^{10B},
C₂₋₆ alkenyl substituted with 0-1 R^{10B},
C₂₋₆ alkynyl substituted with 0-1 R^{10B}, and
C₁₋₆ alkoxy;
- 20 R^{10B} is selected from
C₁₋₄ alkoxy,
C₃₋₆ cycloalkyl,
C₃₋₆ carbocyclic residue substituted with 0-3 R³³,
25 phenyl substituted with 0-3 R³³, and
5-6 membered heterocyclic ring system containing 1, 2,
or 3 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-2
R⁴⁴;
- 30 R¹¹ is selected from
H, halo, -CF₃, -OCF₃, -OH, -OCH₃, -CN, -NO₂, -NR⁴⁶R⁴⁷,

- C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl,
C₁₋₆ alkoxy, (C₁₋₄ haloalkyl)oxy,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³,
5 5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;
- 10 OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², CH(=NR¹⁴)NR¹²R¹³,
NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)₂NR¹²R¹³,
and NR¹⁴S(O)₂R¹²;
- 15 R¹², at each occurrence, is independently selected from
C₁₋₄ alkyl,
C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
20 phenyl substituted with 0-5 R³³;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
25 R³¹;
- R¹³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;
- 30 alternatively, R¹² and R¹³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R¹⁴)-;
- R¹⁴, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;

R³¹, at each occurrence, is independently selected from
H, OH, halo, CF₃, methyl, and ethyl;

5 R³³, at each occurrence, is independently selected from
H, OH, halo, CN, NO₂, CF₃, methyl, and ethyl;

R⁴¹, at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, =O,
10 C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴², and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
15 consisting of N, O, and S substituted with 0-3
R⁴⁴;

R⁴², at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, SR⁴⁵, NR⁴⁶R⁴⁷, OR⁴⁸,
20 NO₂, CN, CH(=NH)NH₂, NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
C₃₋₆ cycloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴⁴, and
25 5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴⁴;

30 R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;

R⁴⁴, at each occurrence, is independently selected from H,
halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂,
C₁₋₄ alkyl, and C₁₋₄ alkoxy;

R⁴⁵ is C₁₋₄ alkyl;

5 R⁴⁶, at each occurrence, is independently selected from H
and C₁₋₃ alkyl;

R⁴⁷, at each occurrence, is independently selected from H,
C₁₋₄ alkyl, -C(=O)NH(C₁₋₄ alkyl), -SO₂(C₁₋₄ alkyl),
-SO₂(phenyl), -C(=O)O(C₁₋₄ alkyl), -C(=O)(C₁₋₄ alkyl),
10 and -C(=O)H;

R⁴⁸, at each occurrence, is independently selected from H,
C₁₋₄ alkyl, -C(=O)NH(C₁₋₄ alkyl), -C(=O)O(C₁₋₄ alkyl),
-C(=O)(C₁₋₄ alkyl), and -C(=O)H;

15

k is 1 or 2;

m is 0, 1, 2; and

20 n is 1 or 2.

[12] In more preferred embodiment of the present
invention,

25

X is -NR^{10A}-;

R¹ is selected from

30 C₂₋₄ alkyl substituted with Z,
C₂₋₄ alkenyl substituted with Z,
C₂₋₄ alkynyl substituted with Z,
C₃₋₆ cycloalkyl substituted with Z,
aryl substituted with Z,

5-6 membered heterocyclic ring system containing at least one heteroatom selected from the group consisting of N, O, and S, said heterocyclic ring system substituted with Z;

5 C₂₋₄ alkyl substituted with 0-2 R², and
C₂₋₄ alkenyl substituted with 0-2 R²;

Z is selected from H,
-CH(OH)R²,
10 -C(ethylenedioxy)R²,
-OR²,
-SR²,
-NR²R³,
-C(O)R²,
15 -C(O)NR²R³,
-NR³C(O)R²,
-C(O)OR²,
-S(O)R²,
-S(O)₂R²,
20 -S(O)₂NR²R³, and -NR³S(O)₂R²;

R², at each occurrence, is independently selected from
phenyl substituted with 0-5 R⁴²;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R⁴¹, and
25 5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴¹;

30 R³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, and
C₁₋₄ alkoxy;

alternatively, R² and R³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R⁴)-;

5 R⁴, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;

R⁵ is H;

10 R^{6a} is selected from H, -OH, -CF₃, methyl, ethyl, propyl,
butyl, methoxy, and, ethoxy;

R^{6b} is H;

15 R⁷, R⁸, and R⁹, at each occurrence, are independently
selected from
H, halo, -CF₃, -OCF₃, -OH, -OCH₃, -CN, -NO₂,
C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, (C₁₋₃
haloalkyl)oxy, and
C₁₋₄ alkyl substituted with 0-2 R¹¹;

20 R^{10A} is selected from H, C₁₋₆ alkyl, C₁₋₄ alkoxy, and
C₁₋₂ alkyl substituted with 0-1 R^{10B};

25 R^{10B} is C₃₋₆ cycloalkyl or
phenyl substituted with 0-3 R³³;

30 R¹¹ is selected from
H, halo, -CF₃, -OCF₃, -OH, -OCH₃, -CN, -NO₂,
C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, and (C₁₋₃
haloalkyl)oxy;

R³³, at each occurrence, is independently selected from
H, OH, halo, CF₃, and methyl;

- R⁴¹, at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, =O,
C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
5 aryl substituted with 0-3 R⁴², and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴⁴;
- 10 R⁴², at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, SR⁴⁵, NR⁴⁶R⁴⁷, OR⁴⁸,
NO₂, CN, CH(=NH)NH₂, NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
15 C₃₋₆ cycloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴⁴, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
20 consisting of N, O, and S substituted with 0-3
R⁴⁴;
- R⁴³ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
phenyl, or pyridyl, each substituted with 0-3 R⁴⁴;
- 25 R⁴⁴, at each occurrence, is independently selected from H,
halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂,
methyl, ethyl, propyl, butyl, methoxy, ethoxy,
propoxy, and butoxy;
- 30 R⁴⁵ is methyl, ethyl, propyl, or butyl;
- R⁴⁶, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;

R⁴⁷, at each occurrence, is independently selected from
H, methyl, ethyl, n-propyl, i-propyl, n-butyl,
i-butyl, -C(=O)NH(methyl), -C(=O)NH(ethyl),
5 -SO₂(methyl), -SO₂(ethyl), -SO₂(phenyl),
-C(=O)O(methyl), -C(=O)O(ethyl), -C(=O)(methyl),
-C(=O)(ethyl), and -C(=O)H;

R⁴⁸, at each occurrence, is independently selected from
10 H, methyl, ethyl, n-propyl, i-propyl, -
C(=O)NH(methyl), -C(=O)NH(ethyl), -C(=O)O(methyl), -
C(=O)O(ethyl), -C(=O)(methyl), -C(=O)(ethyl), and -
C(=O)H;

15 k is 1;

m is 0, 1, or 2; and

n is 1 or 2.

20

[13] In an even more preferred embodiment of the
present invention,

X is -NH-;

25

R¹ is selected from

ethyl substituted with Z,
propyl substituted with Z,
butyl substituted with Z,
30 propenyl substituted with Z,
butenyl substituted with Z,
ethyl substituted with R²,
propyl substituted with R²,
butyl substituted with R²,
35 propenyl substituted with R², and

butenyl substituted with R^2 ;

Z is selected from H,

- CH(OH) R^2 ,
 - 5 -OR 2 ,
 - SR 2 ,
 - NR 2 R 3 ,
 - C(O) R^2 ,
 - C(O)NR 2 R 3 ,
 - 10 -NR 3 C(O) R^2 ,
 - C(O)OR 2 ,
 - S(O) R^2 ,
 - S(O) $_2$ R 2 ,
 - S(O) $_2$ NR 2 R 3 , and -NR 3 S(O) $_2$ R 2 ;
 - 15
- R^2 , at each occurrence, is independently selected from
- phenyl substituted with 0-3 R^{42} ;
 - naphthyl substituted with 0-3 R^{42} ;
 - cyclopropyl substituted with 0-3 R^{41} ;
 - 20 cyclobutyl substituted with 0-3 R^{41} ;
 - cyclopentyl substituted with 0-3 R^{41} ;
 - cyclohexyl substituted with 0-3 R^{41} ;
 - pyridyl substituted with 0-3 R^{41} ;
 - indolyl substituted with 0-3 R^{41} ;
 - 25 indolinyl substituted with 0-3 R^{41} ;
 - benzimidazolyl substituted with 0-3 R^{41} ;
 - benzotriazolyl substituted with 0-3 R^{41} ;
 - benzothienyl substituted with 0-3 R^{41} ;
 - benzofuranyl substituted with 0-3 R^{41} ;
 - 30 phthalimid-1-yl substituted with 0-3 R^{41} ;
 - inden-2-yl substituted with 0-3 R^{41} ;
 - 2,3-dihydro-1H-inden-2-yl substituted with 0-3 R^{41} ;
 - indazolyl substituted with 0-3 R^{41} ;

tetrahydroquinolinyl substituted with 0-3 R⁴¹; and
tetrahydro-isoquinolinyl substituted with 0-3 R⁴¹;

5 R³, at each occurrence, is independently selected from
H, methyl, and ethyl;

R⁵ is H;

10 R^{6a} is selected from H, -OH, methyl, and methoxy;

R^{6b} is H;

15 R⁷, R⁸, and R⁹, at each occurrence, are independently
selected from H, F, Cl, methyl, ethyl, methoxy, -CF₃,
and -OCF₃;

20 R⁴¹, at each occurrence, is independently selected from
H, F, Cl, Br, OH, CF₃, NO₂, CN, =O, methyl, ethyl,
propyl, butyl, methoxy, and ethoxy;

25 R⁴², at each occurrence, is independently selected from
H, F, Cl, Br, OH, CF₃, SO₂R⁴⁵, SR⁴⁵, NR⁴⁶R⁴⁷, OR⁴⁸, NO₂,
CN, =O, methyl, ethyl, propyl, butyl, methoxy, and
ethoxy;

R⁴⁵ is methyl, ethyl, propyl, or butyl;

30 R⁴⁶, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;

R⁴⁷, at each occurrence, is independently selected from
H, methyl, ethyl, n-propyl, i-propyl, n-butyl,
i-butyl, -C(=O)NH(methyl), -C(=O)NH(ethyl),

-SO₂(methyl), -SO₂(ethyl), -SO₂(phenyl),
 -C(=O)O(methyl), -C(=O)O(ethyl), -C(=O)(methyl),
 -C(=O)(ethyl), and -C(=O)H;

5 R⁴⁸, at each occurrence, is independently selected from
 H, methyl, ethyl, n-propyl, i-propyl, -
 C(=O)NH(methyl), -C(=O)NH(ethyl), -C(=O)O(methyl), -
 C(=O)O(ethyl), -C(=O)(methyl), -C(=O)(ethyl), and -
 C(=O)H;

10

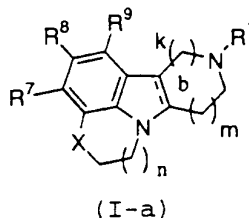
k is 1;

m is 0, 1, or 2; and

15 n is 1 or 2.

[14] In another even more preferred embodiment of the
 present invention, the compound of Formula (I) is selected
 from Formula (I-a):

20



wherein:

25

b is a single bond or a double bond;

X is -NR^{10A}-;

30 R¹ is selected from

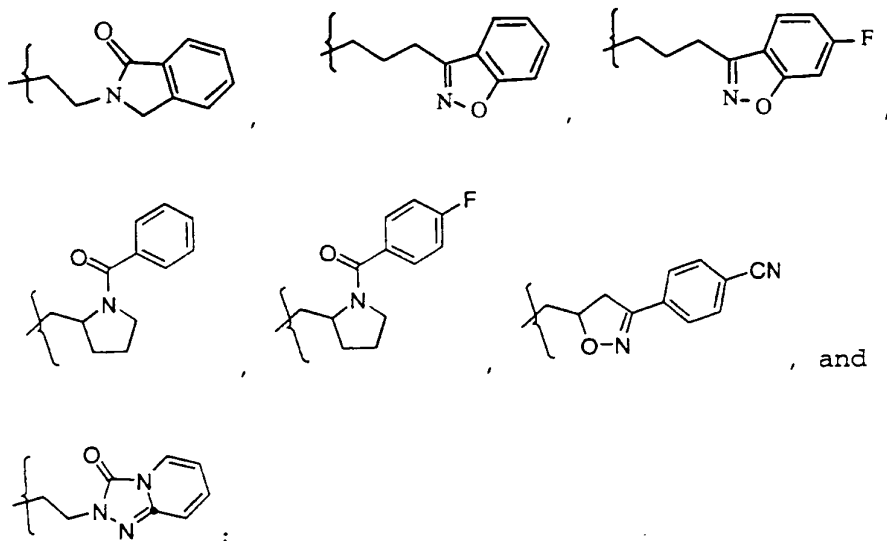
-(CH₂)₃C(=O)(4-fluoro-phenyl),
 -(CH₂)₃C(=O)(4-bromo-phenyl),

- (CH₂)₃C(=O) (4-methyl-phenyl) ,
- (CH₂)₃C(=O) (4-methoxy-phenyl) ,
- (CH₂)₃C(=O) (4-(3,4-dichloro-phenyl)phenyl) ,
- (CH₂)₃C(=O) (3-methyl-4-fluoro-phenyl) ,
- 5 - (CH₂)₃C(=O) (2,3-dimethoxy-phenyl) ,
- (CH₂)₃C(=O) (phenyl) ,
- (CH₂)₃C(=O) (4-chloro-phenyl) ,
- (CH₂)₃C(=O) (3-methyl-phenyl) ,
- (CH₂)₃C(=O) (4-t-butyl-phenyl) ,
- 10 - (CH₂)₃C(=O) (3,4-difluoro-phenyl) ,
- (CH₂)₃C(=O) (2-methoxy-5-fluoro-phenyl) ,
- (CH₂)₃C(=O) (4-fluoro-1-naphthyl) ,
- (CH₂)₃C(=O) (benzyl) ,
- (CH₂)₃C(=O) (4-pyridyl) ,
- 15 - (CH₂)₃C(=O) (3-pyridyl) ,
- (CH₂)₃CH(OH) (4-fluoro-phenyl) ,
- (CH₂)₃CH(OH) (4-pyridyl) ,
- (CH₂)₃CH(OH) (2,3-dimethoxy-phenyl) ,
- (CH₂)₃S(3-fluoro-phenyl) ,
- 20 - (CH₂)₃S(4-fluoro-phenyl) ,
- (CH₂)₃S(=O) (4-fluoro-phenyl) ,
- (CH₂)₃SO₂ (3-fluoro-phenyl) ,
- (CH₂)₃SO₂ (4-fluoro-phenyl) ,
- (CH₂)₃O(4-fluoro-phenyl) ,
- 25 - (CH₂)₃O(phenyl) ,
- (CH₂)₃O(3-pyridyl) ,
- (CH₂)₃O(4-pyridyl) ,
- (CH₂)₃O(2-NH₂-phenyl) ,
- (CH₂)₃O(2-NH₂-5-F-phenyl) ,
- 30 - (CH₂)₃O(2-NH₂-4-F-phenyl) ,
- (CH₂)₃O(2-NH₂-3-F-phenyl) ,
- (CH₂)₃O(2-NH₂-4-Cl-phenyl) ,
- (CH₂)₃O(2-NH₂-4-OH-phenyl) ,

- (CH₂)₃O(2-NH₂-4-Br-phenyl),
- (CH₂)₃O(2-NHC(=O)Me-4-F-phenyl),
- (CH₂)₃O(2-NHC(=O)Me-phenyl),
- (CH₂)₃NH(4-fluoro-phenyl),
- 5 - (CH₂)₃N(methyl)(4-fluoro-phenyl),
- (CH₂)₃CO₂(ethyl),
- (CH₂)₃C(=O)N(methyl)(methoxy),
- (CH₂)₃C(=O)NH(4-fluoro-phenyl),
- (CH₂)₂NHC(=O)(phenyl),
- 10 - (CH₂)₂NMeC(=O)(phenyl),
- (CH₂)₂NHC(=O)(2-fluoro-phenyl),
- (CH₂)₂NMeC(=O)(2-fluoro-phenyl),
- (CH₂)₂NHC(=O)(4-fluoro-phenyl),
- (CH₂)₂NMeC(=O)(4-fluoro-phenyl),
- 15 - (CH₂)₂NHC(=O)(2,4-difluoro-phenyl),
- (CH₂)₂NMeC(=O)(2,4-difluoro-phenyl),
- (CH₂)₃(3-indolyl),
- (CH₂)₃(1-methyl-3-indolyl),
- (CH₂)₃(1-indolyl),
- 20 - (CH₂)₃(1-indolinyl),
- (CH₂)₃(1-benzimidazolyl),
- (CH₂)₃(1H-1,2,3-benzotriazol-1-yl),
- (CH₂)₃(1H-1,2,3-benzotriazol-2-yl),
- (CH₂)₂(1H-1,2,3-benzotriazol-1-yl),
- 25 - (CH₂)₂(1H-1,2,3-benzotriazol-2-yl),
- (CH₂)₃(3,4 dihydro-1(2H)-quinolinyl),
- (CH₂)₂C(=O)(4-fluoro-phenyl),
- (CH₂)₂C(=O)NH(4-fluoro-phenyl),
- CH₂CH₂(3-indolyl),
- 30 - CH₂CH₂(1-phthalimidyl),
- (CH₂)₄C(=O)N(methyl)(methoxy),
- (CH₂)₄CO₂(ethyl),
- (CH₂)₄C(=O)(phenyl),

- (CH₂)₄ (cyclohexyl),
- (CH₂)₃CH (phenyl)₂,
- CH₂CH₂CH=C (phenyl)₂,
- CH₂CH₂CH=CMe (4-F-phenyl),
- 5 - (CH₂)₃CH (4-fluoro-phenyl)₂,
- CH₂CH₂CH=C (4-fluoro-phenyl)₂,
- (CH₂)₂ (2,3-dihydro-1H-inden-2-yl),
- (CH₂)₃C(=O) (2-NH₂-phenyl),
- (CH₂)₃C(=O) (2-NH₂-5-F-phenyl),
- 10 - (CH₂)₃C(=O) (2-NH₂-4-F-phenyl),
- (CH₂)₃C(=O) (2-NH₂-3-F-phenyl),
- (CH₂)₃C(=O) (2-NH₂-4-Cl-phenyl),
- (CH₂)₃C(=O) (2-NH₂-4-OH-phenyl),
- (CH₂)₃C(=O) (2-NH₂-4-Br-phenyl),
- 15 - (CH₂)₃ (1H-indazol-3-yl),
- (CH₂)₃ (5-F-1H-indazol-3-yl),
- (CH₂)₃ (7-F-1H-indazol-3-yl),
- (CH₂)₃ (6-Cl-1H-indazol-3-yl),
- (CH₂)₃ (6-Br-1H-indazol-3-yl),
- 20 - (CH₂)₃C(=O) (2-NHMe-phenyl),
- (CH₂)₃ (1-benzothien-3-yl),
- (CH₂)₃ (6-F-1H-indol-1-yl),
- (CH₂)₃ (5-F-1H-indol-1-yl),
- (CH₂)₃ (6-F-2,3-dihydro-1H-indol-1-yl),
- 25 - (CH₂)₃ (5-F-2,3-dihydro-1H-indol-1-yl),
- (CH₂)₃ (6-F-1H-indol-3-yl),
- (CH₂)₃ (5-F-1H-indol-3-yl),
- (CH₂)₃ (5-F-1H-indol-3-yl),
- (CH₂)₃ (9H-purin-9-yl),
- 30 - (CH₂)₃ (7H-purin-7-yl),
- (CH₂)₃ (6-F-1H-indazol-3-yl),
- (CH₂)₃C(=O) (2-NHSO₂Me-4-F-phenyl),
- (CH₂)₃C(=O) (2-NHC(=O)Me-4-F-phenyl),

- (CH₂)₃C(=O) (2-NHC(=O)Me-phenyl),
- (CH₂)₃C(=O) (2-NHCO₂Et-4-F-phenyl),
- (CH₂)₃C(=O) (2-NHC(=O)NHEt-4-F-phenyl),
- (CH₂)₃C(=O) (2-NHCHO-4-F-phenyl),
- 5 - (CH₂)₃C(=O) (2-OH-4-F-phenyl),
- (CH₂)₃C(=O) (2-MeS-4-F-phenyl),
- (CH₂)₃C(=O) (2-NHSO₂Me-4-F-phenyl),
- (CH₂)₂C(Me)CO₂Me,
- (CH₂)₂C(Me)CH(OH) (4-F-phenyl)₂,
- 10 - (CH₂)₂C(Me)CH(OH) (4-Cl-phenyl)₂,
- (CH₂)₂C(Me)C(=O) (4-F-phenyl),
- (CH₂)₂C(Me)C(=O) (2-MeO-4-F-phenyl),
- (CH₂)₂C(Me)C(=O) (3-Me-4-F-phenyl),
- (CH₂)₂C(Me)C(=O) (2-Me-phenyl),
- 15 - (CH₂)₂C(Me)C(=O)phenyl,



20

R⁷, R⁸, and R⁹, at each occurrence, are independently
selected from

- 25 hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl,
propyl, isopropyl, butyl, t-butyl, nitro,

trifluoromethyl, methoxy, ethoxy, isopropoxy,
trifluoromethoxy, phenyl, benzyl,

5 HC(=O)-, methylC(=O)-, ethylC(=O)-, propylC(=O)-,
isopropylC(=O)-, n-butylC(=O)-, isobutylC(=O)-,
secbutylC(=O)-, tertbutylC(=O)-, phenylC(=O)-,

10 methylC(=O)NH-, ethylC(=O)NH -, propylC(=O)NH-,
isopropylC(=O)NH-, n-butylC(=O)NH-, isobutylC(=O)NH-,
secbutylC(=O)NH-, tertbutylC(=O)NH-, phenylC(=O)NH-,

15 methylamino-, ethylamino-, propylamino-, isopropylamino-,
n-butylamino-, isobutylamino-, secbutylamino-,
tertbutylamino-, phenylamino-,

provided that two of substituents R⁷, R⁸, and R⁹, are
independently selected from hydrogen, fluoro, chloro,
bromo, cyano, methyl, ethyl, propyl, isopropyl, butyl, t-
butyl, nitro, trifluoromethyl, methoxy, ethoxy,
20 isopropoxy, and trifluoromethoxy;

R^{10A} is selected from hydrogen, methyl, ethyl, propyl,
isopropyl, butyl, benzyl, 2-chlorobenzyl, 2-
fluorobenzyl, 2-bromobenzyl, 2-methylbenzyl, 2-
25 trifluoromethylbenzyl, 2-methoxybenzyl, 2-
trifluoromethoxybenzyl, 3-chlorobenzyl, 3-
fluorobenzyl, 3-bromobenzyl, 3-methylbenzyl, 3-
trifluoromethylbenzyl, 3-methoxybenzyl, 3-
trifluoromethoxybenzyl, 4-chlorobenzyl, 4-
30 fluorobenzyl, 4-bromobenzyl, 4-methylbenzyl, 4-
trifluoromethylbenzyl, 4-methoxybenzyl, and 4-
trifluoromethoxybenzyl;

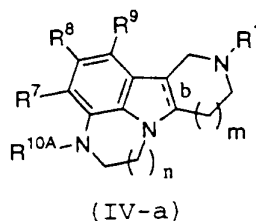
k is 1 or 2;

35

m is 1 or 2; and

n is 1 or 2.

[15] In another even more preferred embodiment of the present invention, the compound of Formula (I) is selected from Formula (IV-a):



10

wherein:

b is a single bond, wherein the bridge hydrogens are in a cis position;

15

R¹ is selected from

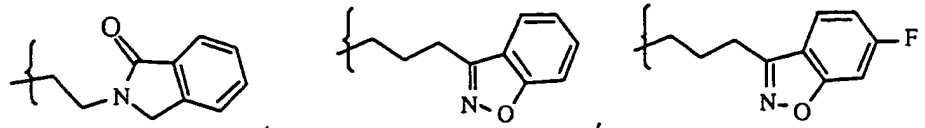
- (CH₂)₃C(=O) (4-fluoro-phenyl),
- (CH₂)₃C(=O) (4-bromo-phenyl),
- (CH₂)₃C(=O) (4-methyl-phenyl),
- 20 - (CH₂)₃C(=O) (4-methoxy-phenyl),
- (CH₂)₃C(=O) (4-(3,4-dichloro-phenyl)phenyl),
- (CH₂)₃C(=O) (3-methyl-4-fluoro-phenyl),
- (CH₂)₃C(=O) (2,3-dimethoxy-phenyl),
- (CH₂)₃C(=O) (phenyl),
- 25 - (CH₂)₃C(=O) (4-chloro-phenyl),
- (CH₂)₃C(=O) (3-methyl-phenyl),
- (CH₂)₃C(=O) (4-t-butyl-phenyl),
- (CH₂)₃C(=O) (3,4-difluoro-phenyl),
- (CH₂)₃C(=O) (2-methoxy-5-fluoro-phenyl),
- 30 - (CH₂)₃C(=O) (4-fluoro-1-naphthyl),
- (CH₂)₃C(=O) (benzyl),

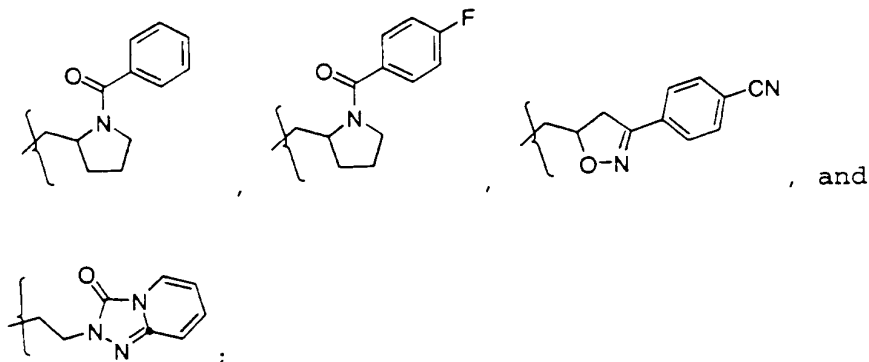
- (CH₂)₃C(=O) (4-pyridyl) ,
- (CH₂)₃C(=O) (3-pyridyl) ,
- (CH₂)₃CH(OH) (4-fluoro-phenyl) ,
- (CH₂)₃CH(OH) (4-pyridyl) ,
- 5 - (CH₂)₃CH(OH) (2,3-dimethoxy-phenyl) ,
- (CH₂)₃S(3-fluoro-phenyl) ,
- (CH₂)₃S(4-fluoro-phenyl) ,
- (CH₂)₃S(=O) (4-fluoro-phenyl) ,
- (CH₂)₃SO₂ (3-fluoro-phenyl) ,
- 10 - (CH₂)₃SO₂ (4-fluoro-phenyl) ,
- (CH₂)₃O (4-fluoro-phenyl) ,
- (CH₂)₃O (phenyl) ,
- (CH₂)₃NH (4-fluoro-phenyl) ,
- (CH₂)₃N (methyl) (4-fluoro-phenyl) ,
- 15 - (CH₂)₃CO₂ (ethyl) ,
- (CH₂)₃C(=O)N (methyl) (methoxy) ,
- (CH₂)₃C(=O)NH (4-fluoro-phenyl) ,
- (CH₂)₂NHC(=O) (phenyl) ,
- (CH₂)₂NMeC(=O) (phenyl) ,
- 20 - (CH₂)₂NHC(=O) (2-fluoro-phenyl) ,
- (CH₂)₂NMeC(=O) (2-fluoro-phenyl) ,
- (CH₂)₂NHC(=O) (4-fluoro-phenyl) ,
- (CH₂)₂NMeC(=O) (4-fluoro-phenyl) ,
- (CH₂)₂NHC(=O) (2,4-difluoro-phenyl) ,
- 25 - (CH₂)₂NMeC(=O) (2,4-difluoro-phenyl) ,
- (CH₂)₃ (3-indolyl) ,
- (CH₂)₃ (1-methyl-3-indolyl) ,
- (CH₂)₃ (1-indolyl) ,
- (CH₂)₃ (1-indolyl) ,
- 30 - (CH₂)₃ (1-benzimidazolyl) ,
- (CH₂)₃ (1H-1,2,3-benzotriazol-1-yl) ,
- (CH₂)₃ (1H-1,2,3-benzotriazol-2-yl) ,
- (CH₂)₂ (1H-1,2,3-benzotriazol-1-yl) ,

- (CH₂)₂ (1H-1,2,3-benzotriazol-2-yl),
- (CH₂)₃ (3,4 dihydro-1(2H)-quinolinyl),
- (CH₂)₂ C(=O) (4-fluoro-phenyl),
- (CH₂)₂ C(=O) NH (4-fluoro-phenyl),
- 5 -CH₂CH₂ (3-indolyl),
- CH₂CH₂ (1-phthalimidyl),
- (CH₂)₄ C(=O) N (methyl) (methoxy),
- (CH₂)₄ CO₂ (ethyl),
- (CH₂)₄ C(=O) (phenyl),
- 10 - (CH₂)₄ (cyclohexyl),
- (CH₂)₃ CH (phenyl)₂,
- CH₂CH₂CH=C (phenyl)₂,
- CH₂CH₂CH=CMe (4-F-phenyl),
- (CH₂)₃ CH (4-fluoro-phenyl)₂,
- 15 -CH₂CH₂CH=C (4-fluoro-phenyl)₂,
- (CH₂)₂ (2,3-dihydro-1H-inden-2-yl),
- (CH₂)₃ C(=O) (2-NH₂-phenyl),
- (CH₂)₃ C(=O) (2-NH₂-5-F-phenyl),
- (CH₂)₃ C(=O) (2-NH₂-4-F-phenyl),
- 20 - (CH₂)₃ C(=O) (2-NH₂-3-F-phenyl),
- (CH₂)₃ C(=O) (2-NH₂-4-Cl-phenyl),
- (CH₂)₃ C(=O) (2-NH₂-4-OH-phenyl),
- (CH₂)₃ C(=O) (2-NH₂-4-Br-phenyl),
- (CH₂)₃ (1H-indazol-3-yl),
- 25 - (CH₂)₃ (5-F-1H-indazol-3-yl),
- (CH₂)₃ (7-F-1H-indazol-3-yl),
- (CH₂)₃ (6-Cl-1H-indazol-3-yl),
- (CH₂)₃ (6-Br-1H-indazol-3-yl),
- (CH₂)₃ C(=O) (2-NHMe-phenyl),
- 30 - (CH₂)₃ (1-benzothien-3-yl),
- (CH₂)₃ (6-F-1H-indol-1-yl),
- (CH₂)₃ (5-F-1H-indol-1-yl),
- (CH₂)₃ (6-F-2,3-dihydro-1H-indol-1-yl),

- (CH₂)₃ (5-F-2,3-dihydro-1H-indol-1-yl),
- (CH₂)₃ (6-F-1H-indol-3-yl),
- (CH₂)₃ (5-F-1H-indol-3-yl),
- (CH₂)₃ (5-F-1H-indol-3-yl),
- 5 - (CH₂)₃ (9H-purin-9-yl),
- (CH₂)₃ (7H-purin-7-yl),
- (CH₂)₃ (6-F-1H-indazol-3-yl),
- (CH₂)₃ C(=O) (2-NHSO₂Me-4-F-phenyl),
- (CH₂)₃ C(=O) (2-NHC(=O)Me-4-F-phenyl),
- 10 - (CH₂)₃ C(=O) (2-NHC(=O)Me-4-F-phenyl),
- (CH₂)₃ C(=O) (2-NHCO₂Et-4-F-phenyl),
- (CH₂)₃ C(=O) (2-NHC(=O)NEt-4-F-phenyl),
- (CH₂)₃ C(=O) (2-NHCHO-4-F-phenyl),
- (CH₂)₃ C(=O) (2-OH-4-F-phenyl),
- 15 - (CH₂)₃ C(=O) (2-MeS-4-F-phenyl),
- (CH₂)₃ C(=O) (2-NHSO₂Me-4-F-phenyl),
- (CH₂)₂ C(Me) CO₂Me,
- (CH₂)₂ C(Me) CH(OH) (4-F-phenyl)₂,
- (CH₂)₂ C(Me) CH(OH) (4-Cl-phenyl)₂,
- 20 - (CH₂)₂ C(Me) C(=O) (4-F-phenyl),
- (CH₂)₂ C(Me) C(=O) (2-MeO-4-F-phenyl),
- (CH₂)₂ C(Me) C(=O) (3-Me-4-F-phenyl),
- (CH₂)₂ C(Me) C(=O) (2-Me-phenyl),
- (CH₂)₂ C(Me) C(=O) phenyl,

25





5 R⁷, R⁸, and R⁹, at each occurrence, are independently selected from hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, nitro, trifluoromethyl, methoxy, ethoxy, isopropoxy, trifluoromethoxy, methylC(=O)-, ethylC(=O)-, propylC(=O)-, isopropylC(=O)-, methylC(=O)NH-, ethylC(=O)NH-, propylC(=O)NH-, isopropylC(=O)NH-, methylamino-, ethylamino-, propylamino-, and isopropylamino-,

15 provided that two of substituents R⁷, R⁸, and R⁹, are independently selected from hydrogen, fluoro, chloro, methyl, trifluoromethyl, methoxy, and trifluoromethoxy;

20 R^{10A} is selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, benzyl, 2-chlorobenzyl, 2-fluorobenzyl, 2-bromobenzyl, 2-methylbenzyl, 2-trifluoromethylbenzyl, 2-methoxybenzyl, 2-trifluoromethoxybenzyl, 3-chlorobenzyl, 3-fluorobenzyl, 3-bromobenzyl, 3-methylbenzyl, 3-trifluoromethylbenzyl, 3-methoxybenzyl, 3-trifluoromethoxybenzyl, 4-chlorobenzyl, 4-fluorobenzyl, 4-bromobenzyl, 4-methylbenzyl, 4-trifluoromethylbenzyl, 4-methoxybenzyl, and 4-trifluoromethoxybenzyl;

m is 1 or 2; and

n is 1 or 2.

5

In an even further more preferred embodiment of the present invention, are compounds of Formula (I) selected from Table 1.

10

In a second embodiment, the present invention provides a pharmaceutical composition comprising a compound of Formula (I) and a pharmaceutically acceptable carrier.

15

In a third embodiment, the present invention provides a method for the treatment a central nervous system disorder comprising administering to a host in need of such treatment a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the compound is a 5HT2a antagonist or a 5HT2c agonist.

20

In a preferred embodiment the compound is a 5HT2a antagonist.

25

In another preferred embodiment the compound is a 5HT2c agonist.

30

In a more preferred embodiment the present invention provides a method for the treatment central nervous system disorders including obesity, anxiety, depression, psychosis, schizophrenia, sleep disorders, sexual disorders, migraine, conditions associated with cephalic pain, social phobias, and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility comprising administering to a host in need of such

35

treatment a therapeutically effective amount of a compound of Formula (I).

In a further preferred embodiment the central nervous system disorder comprises obesity.

In another further preferred embodiment the central nervous system disorder comprises schizophrenia.

In another further preferred embodiment the central nervous system disorder comprises depression.

In another further preferred embodiment the central nervous system disorder comprises anxiety.

In a fourth embodiment the present invention provides novel compounds of Formula (I) or pharmaceutically acceptable salt forms thereof for use in therapy.

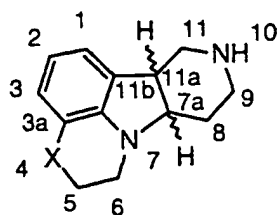
In a fifth embodiment the present invention provides the use of novel compounds of Formula (I) or pharmaceutically acceptable salt forms thereof for the manufacture of a medicament for the treatment of central nervous system disorders including obesity, anxiety, depression, psychosis, schizophrenia, sleep disorders, sexual disorders, migraine, conditions associated with cephalic pain, social phobias, and gastrointestinal disorders.

DEFINITIONS

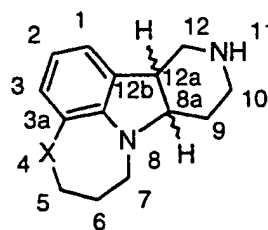
The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by

resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

The numbering of the tetracyclic ring-system present in the compounds of Formula (I), as defined by nomenclature known to one skilled in the art, is shown for two examples in Formula (I'), when k is 1, m is 1, and n is 1; and in Formula (I''), when k is 1, m is 1, and n is 2:



(I')



(I'')

20

The tetracyclic ring-system present in compounds of Formula (I) occur as "cis" or "trans" isomers when the carbon-carbon bond b in Formula (I) is a single bond. As such, the terms "cis" and "trans", in conjunction with the tetracyclic ring structure, refer to the configuration of hydrogen atoms on carbon atoms 7a and 11a in Formula (I') or, for example, on carbon atoms 8a and 12a in Formula (I''), above. When both hydrogens are on the same side of the mean plane determined by the octahydro tetracyclic moiety then the configuration is designated "cis", if not, the configuration is designated "trans". It is understood

30

that the above example is for demonstrative purposes only and not intended to limit the scope of the tetracyclic ring-system present in compounds of Formula (I). As such, it is understood that one skilled in the art of organic chemistry can apply the above numbering system to other values of k, m, and n in the scope of compounds of Formula (I) to determine the appropriate numbering. Additional Examples of the numbering of the tetracyclic ring-system are further provided below in the synthetic Examples.

10 Lastly, it is understood that the use of "cis" or "trans" in the identification of the tetracyclic ring-system is not meant to construe the configuration of any other cis or trans geometric isomer in the molecule, for example, cis or trans butene.

15 The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a

20 substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

When any variable (e.g., R^2) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example,

25 if a group is shown to be substituted with 0-2 R^2 , then said group may optionally be substituted with up to two R^2 groups and R^2 at each occurrence is selected independently from the definition of R^2 . Also, combinations of

30 substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is

35 listed without indicating the atom via which such

substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations
5 result in stable compounds.

As used herein, "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; for example, "C₁-C₆ alkyl" denotes alkyl
10 having 1 to 6 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, n-hexyl, 2-methylbutyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, and 4-methylpentyl.

15 "Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either a straight or branched configuration having the specified number of carbon atoms and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain. Examples of
20 alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, 4-methyl-3-pentenyl, and the like.

25 "Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more carbon-carbon triple bonds which may occur in any stable point along the chain, such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the
30 like.

"Cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms. For example, "C₃-C₆ cycloalkyl" denotes such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

"Alkoxy" or "alkyloxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, 5 n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. Similarly, "alkylthio" is represents an alkyl group as defined above with the indicated number of carbon atoms attached through a sulpher bridge.

10 "Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, and the like.

15 "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where $v = 1$ to 3 and $w = 1$ to $(2v+1)$). Examples of haloalkyl include, but 20 are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl.

As used herein, "carbocycle" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 25 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, 30 [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heterocyclic ring" is intended to mean a stable 5- to 7- 35 membered monocyclic or bicyclic or 7- to 14-membered bicyclic heterocyclic ring which is saturated partially

unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the

5 above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings

10 described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1,

15 then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidinyl, 2H,6H-1,5,2-dithiazinyl,

20 2H-pyrrolyl, 3H-indolyl, 4-piperidinyl, 4aH-carbazole, 4H-quinoliziny, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazoliny, benzthiazolyl, benztriazolyl, benztetrazolyl,

25 benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, b-carboliny, chromanyl, chromenyl, cinnoliny, decahydroquinoliny, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, imidazolopyridiny, 1H-indazolyl, indolenyl, indoliny, indoliziny, indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny, isoindolyl, isoquinoliny, isothiazolyl,

30 isothiazolopyridiny, isoxazolyl, isoxazolopyridiny, morpholiny, naphthyridiny, octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl,

1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl,
oxazolyl, oxazolopyridinyl, oxazolidinylperimidinyl,
oxindolyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl,
phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl,
5 phthalazinyl, piperazinyl, piperidinyl, pteridinyl,
piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl,
pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolopyridinyl,
pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole,
pyridothiazole, pyridinyl, pyridyl, pyrimidinyl,
10 pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl,
quinolinyl, 4H-quinolizinyll, quinoxalinyl, quinuclidinyl,
carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl,
tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl,
1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl,
15 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl,
thiazolopyridinyl, thienyl, thienothiazolyl,
thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl,
1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl,
1,3,4-triazolyl, and xanthenyl. Preferred heterocycles
20 include, but are not limited to, pyridinyl, furanyl,
thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl,
imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl,
oxazolidinyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl,
oxindolyl, benzoxazolinyll, benzthiazolyl, benzisothiazolyl,
25 isatinoyl, isoxazolopyridinyl, isothiazolopyridinyl,
thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl,
and pyrazolopyridinyl. Preferred 5 to 6 membered
heterocycles include, but are not limited to, pyridinyl,
furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl,
30 piperazinyl, imidazolyl, and oxazolidinyl. Also included
are fused ring and spiro compounds containing, for example,
the above heterocycles.

As used herein, the term "bicyclic heterocyclic ring
system" is intended to mean a stable 9- to 10-membered
35 bicyclic heterocyclic ring formed from the substituent
NR¹²R¹³, which is partially unsaturated or unsaturated

(aromatic), and which consists of carbon atoms, a nitrogen atom, and 1 or 2 additional heteroatoms independently selected from the group consisting of N, O and S. The additional nitrogen or sulfur heteroatoms may optionally be
5 oxidized. The heterocyclic ring is attached to its pendant group by the nitrogen atom of the group $NR^{12}R^{13}$ and for which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If
10 specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the
15 heterocycle is not more than 1. The term "bicyclic heterocyclic ring system" is intended to be a subset of the term "heterocyclic ring system". Preferred examples of a 9- to 10- membered bicyclic heterocyclic ring system are benzimidazolyl, benzimidazolinyl, benzoxazolinyl,
20 dihydrobenzthiazolyl, dihydrodioxobenzthiazolyl, benzisoxazolinyl, 1H-indazolyl, indolyl, indolinyl, isoindolinyl, tetrahydro-isoquinolinyl, tetrahydro-quinolinyl, and benzotriazolyl.

25 Additionally, a subclass of preferred heterocycles are heterocycles which function as an isostere of a cyclic but non-heterocyclic substituent such as $-CH_2-C(=O)-phenyl$. Preferred examples of such heterocycles include, but are not limited to, benzimidazolyl, benzofuranyl,
30 benzothiophenyl, benzoxazolyl, benzthiazolyl, benzisoxazolyl, furanyl, imidazolinyl, 1H-indazolyl, indolinyl, isoindolinyl, isoquinolinyl, oxazolyl, piperidinyl, pyrazinyl, pyridinyl, pyrimidinyl, quinolinyl, thiazolyl, thiophenyl, and 1,2,3-triazolyl.

As used herein, the term "aryl", or aromatic residue, is intended to mean an aromatic moiety containing the specified number of carbon atoms, such as phenyl, pyridinyl and naphthyl.

5 The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals
10 without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the
15 parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the
20 like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from
25 inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic,
30 phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present
35 invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical

methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are intended to include any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula (I) are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug or compound of formula (I) is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of Formula (I), and the like.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

SYNTHESIS

Throughout the details of the invention, the following abbreviations are used with the following meanings:

5 Reagents:

	MCPBA	m-chloroperoxybenzoic acid
	DIBAL	diisobutyl aluminum hydride
	Et ₃ N	triethylamine
	TFA	trifluoroacetic acid
10	LAH	lithium aluminum hydride
	NBS	N-bromo succinimide
	Red-Al	Sodium bis(2-methoxyethoxy)aluminum hydride
	Pd ₂ dba ₃	Tris(dibenzylideneacetone)dipalladium(0)
	ACE-Cl	2-chloroethylchloroformate

15

Solvents:

	THF	tetrahydrofuran
	MeOH	methanol
	EtOH	ethanol
20	EtOAc	ethyl acetate
	HOAc	acetic acid
	DMF	dimethyl formamide
	DMSO	dimethyl sulfoxide
	DME	dimethoxyethane
25	Et ₂ O	diethylether
	iPrOH	isopropanol
	MEK	methyl ethyl ketone

Others:

30	Ar	aryl
	Ph	phenyl
	Me	methyl
	Et	ethyl
	NMR	nuclear magnetic resonance
35	MHz	megahertz

	BOC	tert-butoxycarbonyl
	CBZ	benzyloxycarbonyl
	Bn	benzyl
	Bu	butyl
5	Pr	propyl
	cat.	catalytic
	mL	milliliter
	nM	nanometer
	ppm	part per million
10	mmol	millimole
	mg	milligram
	g	gram
	kg	kilogram
	TLC	thin layer chromatography
15	HPLC	high pressure liquid chromatography
	RPM	revolutions per minute
	rt	room temperature
	aq.	aqueous
	sat.	saturated

20

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

30

The novel compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below,

35

it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

The preparation of compounds of Formula (I) of the present invention may be carried out in a convergent or sequential synthetic manner. Detailed synthetic preparations of the compounds of Formula (I) are shown in the following reaction schemes. The skills required in preparation and purification of the compounds of Formula (I) and the intermediates leading to these compounds are known to those in the art. Purification procedures include, but are not limited to, normal or reverse phase chromatography, crystallization, and distillation.

Several methods for the preparation of the compounds of the present invention are illustrated in the schemes and examples shown below. The substitutions are as described and defined above.

Compounds of Formula (I) of this invention may be prepared as shown in Scheme 1. Thus, preparation of an aryl hydrazine (III) is accomplished, for example, by treatment of a corresponding substituted aniline (II) with NaNO_2 followed by reduction of the N-nitroso intermediate with a reducing agent such as LAH or zinc and an organic acid, such as acetic acid or trifluoroacetic acid at low temperature. Assembly of the core tetracyclic intermediate indole (V) is accomplished by Fischer indole cyclization of

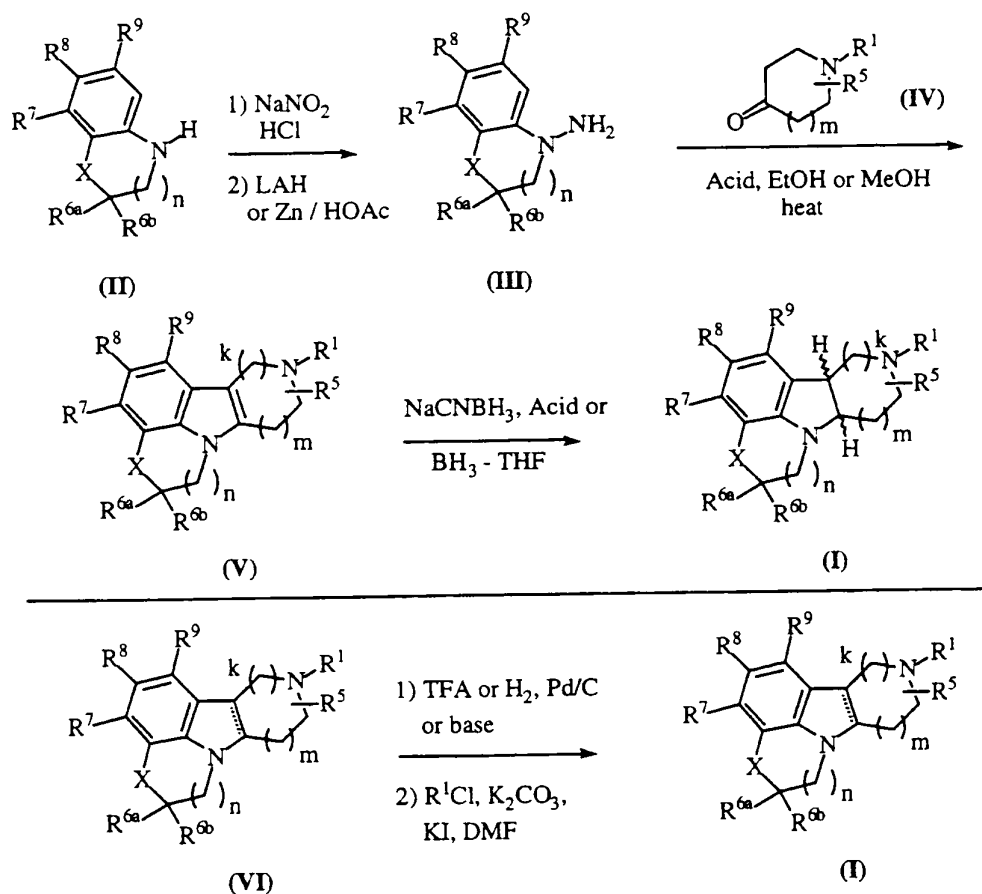
the aryl hydrazine and a suitably substituted ketone (i.e. (IV)) by methods described by, but not limited to, R.J. Sundberg, "Indoles, Best Synthetic Methods" 1996, Academic Press, San Diego, CA. For example, treatment of the aryl
5 hydrazine (III) as the free base or the corresponding mineral acid salt with the ketone (IV) ($R^1 = H, Bn, CBZ, CO_2Et$, etc) in an alcoholic solvent in the presence of mineral acid affords the indoles (V) as the free bases (after treatment with aq. NaOH). Reduction of the indoles
10 to the corresponding cis or trans substituted dihydroindoles is accomplished by, for example, treatment with hydrogen in the presence of a catalyst such as platinum oxide or palladium on carbon, or with a metal such as zinc and a mineral acid such as hydrochloric acid, or
15 with sodium and liquid ammonia, or with borane-amine complex such as borane-triethylamine in tetrahydrofuran, or preferably by treatment with $NaCNBH_3$ in an acid such as acetic or trifluoroacetic acid.

The corresponding enantiomers can be isolated by
20 separation of the racemic mixture of (I) on a chiral stationary phase column utilizing normal or reverse phase HPLC techniques, the details of which are described in the examples. Alternatively, a diastereomeric mixture of (I) can be prepared by treatment of (I, $R^1 = H$) with an
25 appropriate chiral acid (or suitably activated derivative), for example dibenzoyl tartrate or the like (see, for example, Kinbara, K., et. al., *J. Chem. Soc., Perkin Trans. 2*, 1996, 2615; and Tomori, H., et. al., *Bull. Chem. Soc. Jpn.*, 1996, 3581). The diastereomers would then be
30 separated by traditional techniques (i.e. silica chromatography, crystallization, HPLC, etc) followed by removal of the chiral auxiliary to afford enantiomerically pure (I).

In the cases where the carboline nitrogen has been
35 protected (VI) (i.e. $R^1 = Boc, Bn, CBZ, CO_2R$), it may be

removed under a variety of conditions as described in Greene, T.W., Wuts, P.G.W., "Protective Groups in Organic Synthesis, 2nd Edition", John Wiley and Sons, Inc., New York, pages 309-405, 1991. The free secondary amine could then be alkylated, for example, by treatment with a suitably substituted alkyl halide (R^1Cl , or R^1I) and a base to afford additional compounds of type (I), as described, for example, by Glennon, R.A., et. al., *Med. Chem. Res.*, 1996, 197.

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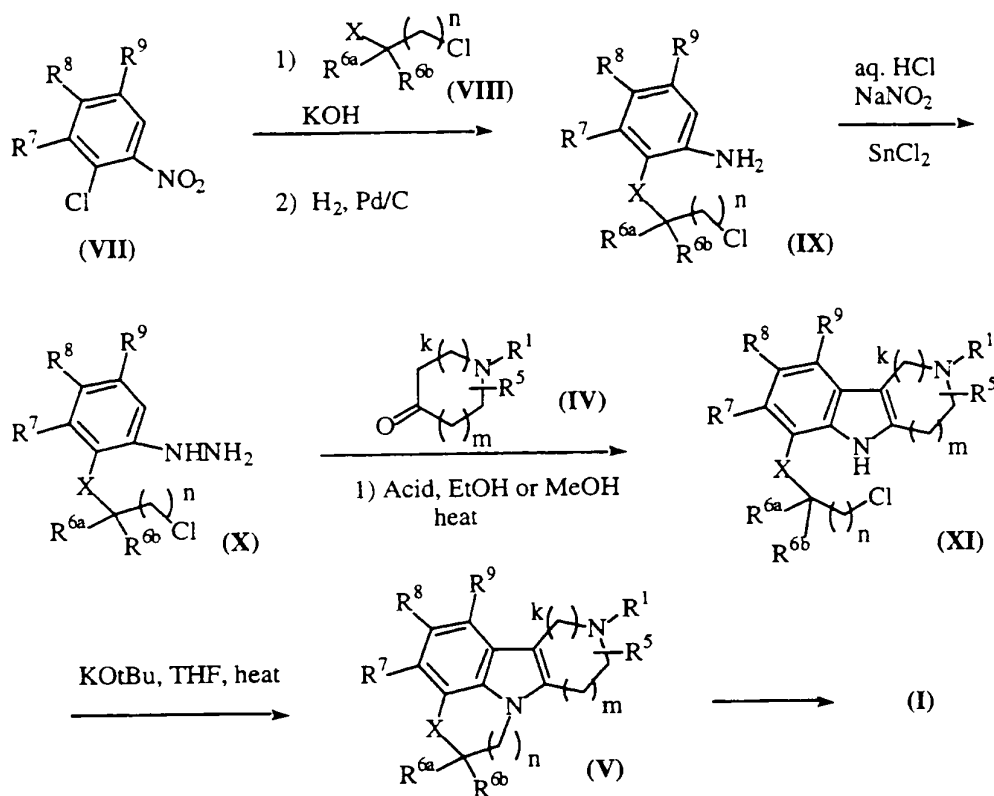
SCHEME 1

Alternatively, compounds of Formula (I) can be prepared as described in Scheme 2. Treatment of an ortho

halonitrobenzene compound (VII) with a nucleophilic alkyl halide ($X = OH, SH, NHR, (VIII)$) (as described by Kharasch, N., Langford, R.B., *J. Org. Chem.*, **1963**, 1903) and a suitable base followed by subsequent reduction of the corresponding nitroaryl derivative to the aniline (IX). The reduction may be accomplished with a variety of reducing agents, for example, LAH, $SnCl_2$, $NaBH_4$, N_2H_4 , etc. or with hydrogen in the presence of a suitable catalyst, such as palladium on carbon, or platinum oxide, etc., (see Hudlicky, M., "Reductions in Organic Chemistry", Ellis Horwood, Ltd., Chichester, UK, **1984**). Formation of the aryl hydrazine (X) may be accomplished as described previously in Scheme 1 or more directly by treatment of the aniline (IX) with aq. hydrochloric acid, stannous chloride and $NaNO_2$ at room temperature (see, Buck, J.S., Ide, W.S., *Org. Syn., Coll. Vol.*, **2**, **1943**, 130). This primary aryl hydrazine (X) can then be cyclized under Fischer indole cyclization conditions as detailed above for compound (V); to afford the indole (XI) as the corresponding salt. Upon treatment of the indole (XI) with a base such potassium hydroxide or potassium t-butoxide in a solvent such as DME or THF affords the tetracyclic indole intermediates (V). These indoles can also be reduced to the corresponding cis or trans indolines (I) as described previously in Scheme 1.

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SCHEME 2

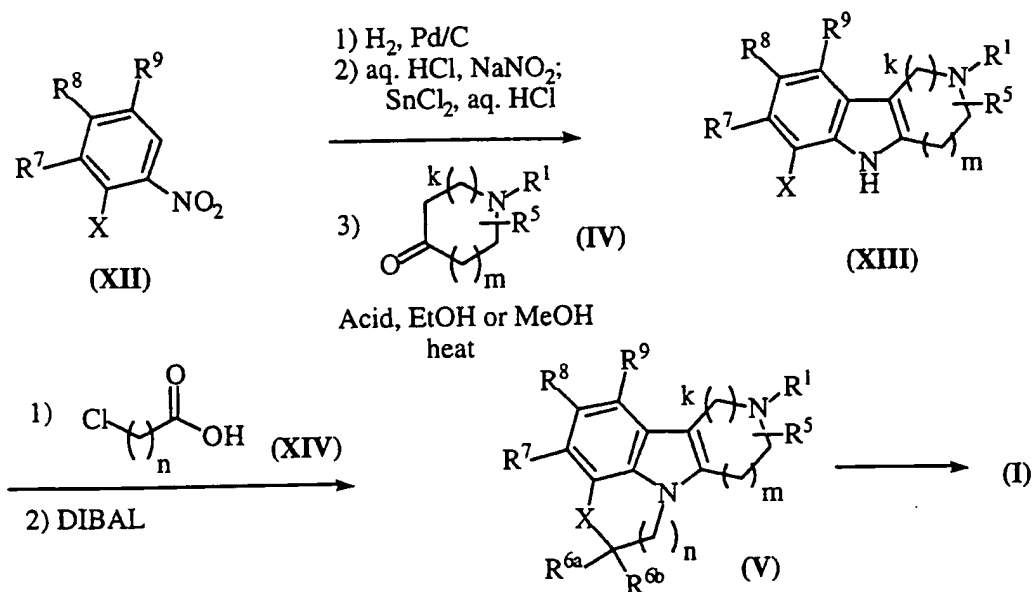


Still another related route to compounds of Formula (I) is shown in Scheme 3. Initiating the synthesis with a nitrobenzene derivative such as (XII), this approach allows for a variety of derivatization. More highly substituted nitrobenzenes can be obtained by traditional synthetic manipulation (*i.e.* aromatic substitution) and are known by those in the art (see Larock, R.C., *Comprehensive Organic Transformations*, VCH Publishers, New York, **1989**).

Treatment of nitrobenzene derivative with a reducing agent such as LAH, etc., as described previously (see Hudlicky, et. al.), affords the corresponding aniline intermediate. Subsequent formation of the hydrazine followed by Fischer indole cyclization with a suitably functionalized ketone as described above (*i.e.* Scheme 1, (III) to (V)) affords the

g-carboline indole (XIII). At this point the fused ring may be appended by condensation of a haloalkyl carboxylic acid or a related activated carboxylic acid (i.e. acid chloride, mixed anhydride, etc.) such as (XIV). Reduction of the resultant heterocyclic carbonyl may be effected with various reducing agents, for example, sodium borohydride, diisobutyl aluminum hydride and the like (see Larock, R.C., *Comprehensive Organic Transformations*, VCH Publishers, New York, 1989 and/or Hudlicky, M., "Reductions in Organic Chemistry", Ellis Horwood, Ltd., Chichester, UK, 1984) to afford the tetracyclic indoles (V). Further reduction of the indole (V) to the indolines (I) is as described previously in Scheme 1.

SCHEME 3

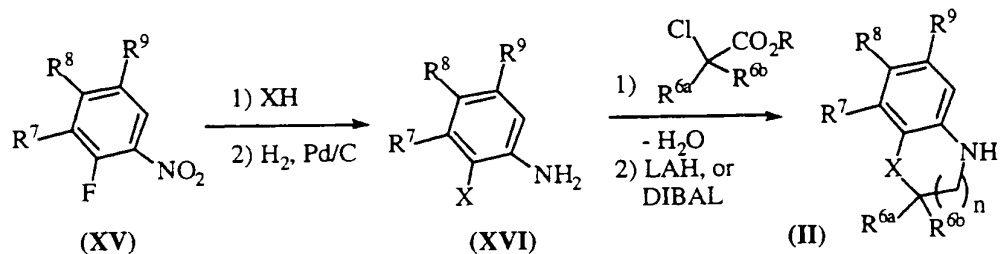


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Preparation of the aniline precursors (II) to the Fischer indole cyclizations is shown in Scheme 4. Treatment of a suitably ortho-functionalized aniline (XVI) with a chloroalkyl carboxylic acid or ester (or equivalent substrate, i.e. acrylic acid, acryloyl chloride, etc.) and concomitant condensation, followed by reduction of the

resultant heterocyclic carbonyl with a reducing agent such as LAH, DIBAL, or Red-Al affords the fused heterocyclic benzene derivatives (II). More diverse intermediates of (II) may be obtained by formation of the ortho substituted aniline from the corresponding ortho substituted nitobenzenes and concomitant reduction of the nitro moiety as described above. Furthermore, aromatic substitution of the fluoro (or other halo derived nitrobenzene) functionality of (XV) for an oxygen, or sulphur moiety is accomplished, for example, by treatment of (XV) with a nucleophile, such as sodium sulfide or an alcohol, followed by formation of the requisite thiophenol or phenol, respectively, using standard techniques known by those in the art (see Larock, R.C., *Comprehensive Organic Transformations*, VCH Publishers, New York, 1989, page 481). Reduction of the nitro as before affords the substituted anilines (XVI).

SCHEME 4

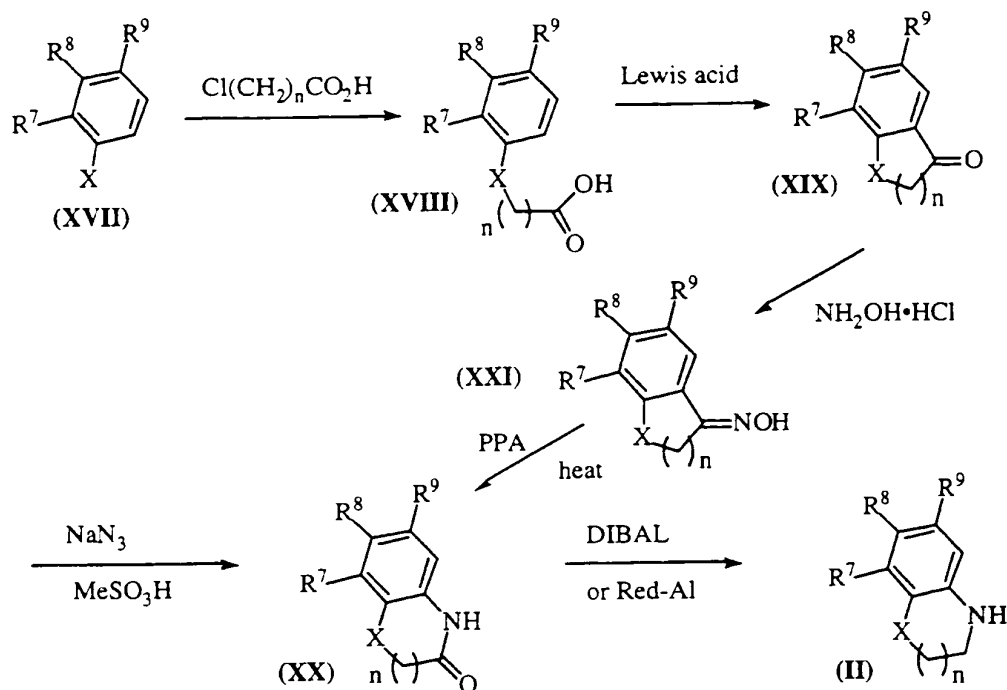


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An alternate approach to the substituted fused anilines (II) is shown in Scheme 5. Treatment of the phenol (X = OH), thiophenol (X = SH), or other nucleophilically aromatic substituted derivative (XVII) with, for example, a haloalkyl carboxylic acid (or equivalent activated haloalkylcarboxylic acid, (i.e. acid halide, mixed anhydride, acrylic acid, acryloyl chloride, etc.)), affords the derivative (XVIII) which when treated under Friedel-Crafts acylation conditions (see Ed. G.A.

Olah, "Friedel-Crafts and Related Reactions", J. Wiley and Sons, New York, 1964, Vol 3, Pts 1 and 2 or Chem. Rev., 1955, 229, or Olah, G.A., "Friedel-Crafts Chemistry", Wiley Interscience, New York, 1973, for varying conditions and
5 protocols), i.e. strong Lewis acids (AlCl_3 , FeCl_3 , etc.), affords the cyclic alkylphenones (XIX). Incorporation of the nitrogen functionality can be accomplished in several ways. For example, Schmidt rearrangement (as described by Smith, P.A.S., *J. Am. Chem. Soc.*, 1948, 320) is effected by
10 treatment of the carbonyl derivative (XIX) with NaN_3 and methanesulfonic acid to afford the bicyclic lactam (XX). Alternatively, this transformation may be carried out under Hoffmann rearrangement protocol (see, for example, Dike, S.Y., et. al., *Bioorg. Med. Chem. Lett.*, 1991, 383), by
15 initial formation of the oxime derivative of (XXI) by treatment with hydroxylamine hydrochloride. Subsequent rearrangement to the lactam is efficiently accomplished by heating in polyphosphoric acid to afford the lactam (XX). Reduction of the lactam (XX) can be accomplished with a
20 variety of reducing agents, for example, DIBAL, Red-Al and the like to afford the aniline (II).

SCHEME 5

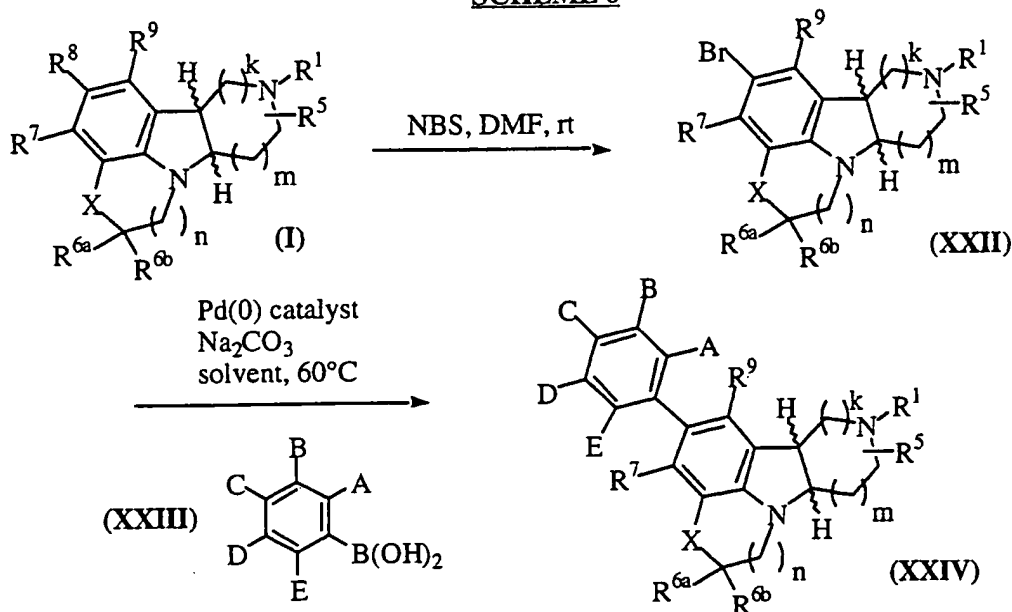


The preparation of compounds of Formula (I) with additional diversity of functionalization of the aromatic A ring of the tetracycle is shown in Scheme 6 and Scheme 7 and described here. Due to the nature of the synthetic route of Scheme 1 to derivatives of Formula (I), compounds with halogen substituents on the A-ring are difficult to prepare. However, bromination of the indolines (I, R⁸ = H) when the amine is protected, for example, with the Boc or CBZ protecting groups, with, for example, NBS in DMF affords the R⁸ brominated derivatives (XXII). These activated aryl derivatives (XXII) act as excellent counterparts for a number of important synthetic transformations.

For example, biaryl coupling is accomplished under Suzuki coupling protocol. For a review and leading references of palladium catalyzed cross coupling reactions,

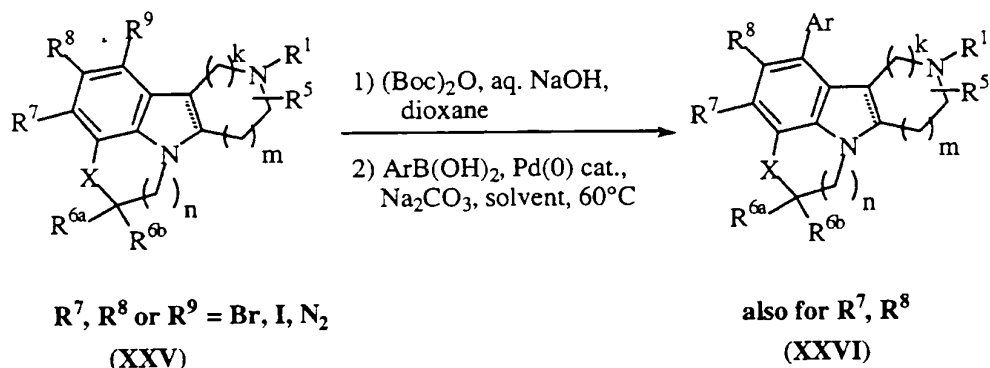
see Miyaura, N., Suzuki, A., *Chem. Rev.*, **1995**, 2457. One such procedure entails treatment of the aryl bromide (XXII) with a functionalized aryl boronic acid (XXIII) in the presence of a catalytic Pd(0) species, such as Pd(PPh₃)₄, Pd(PPh₃)₂Cl₂, Pd(OAc)₂, Pd₂(dba)₃ and a suitable ligand such as PPh₃, AsPh₃, etc., or other such Pd(0) catalyst, and a base such as Na₂CO₃ or Et₃N in a suitable solvent such as DMF, toluene, THF, DME or the like, to afford the indolines (XXIV). Alternatively formation of the indole boronic acid from the bromine derivative (XXII) (i.e. (I, R⁸ = B(OH)₂)) would allow for greater diversity in the subsequent coupling of this indole boronic acid with commercially available haloaromatic derivatives in a similar Suzuki coupling strategy as described above to afford the indolines (XXIV).

SCHEME 6



Similarly biaryl coupling of the bromine derivatives (XXV), readily obtained by the synthetic sequence exemplified in Scheme 2, (starting with the suitably functionalized bromo nitrobenzenes (II)), is shown in

Scheme 7. This approach allows for the preparation of biaryl indoles as well as the corresponding indoline derivatives. Protection of the amine functionality must be carried out if $R^1 = H$ (see Greene et.al for protections of amines). This is readily accomplished, for example, by treatment of bromo derivatives (XXV) with $(Boc)_2O$ in aqueous sodium hydroxide and dioxane. Subsequent Suzuki coupling with a variety of aryl boronic acids is carried out as described above in Scheme 6, to afford the biaryl adducts (XXVI). This protocol is amenable to R^7 , R^8 , and R^9 bromide, iodide, triflates, and/or diazo derivatives (see Miyaura, N., Suzuki, A., *Chem. Rev.*, **1995**, 2457, for a review of aryl couplings).

SCHEME 7

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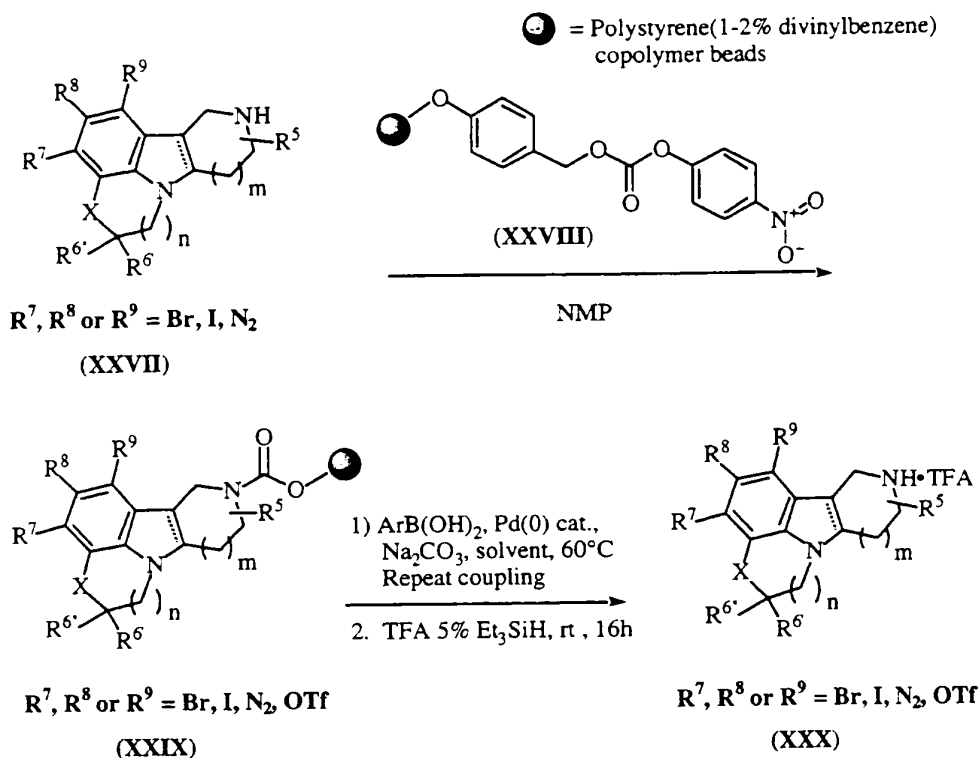
Furthermore and as an extension of this approach to a rapid preparation of a large array of biaryl indole and indoline derivatives, these bromide derivatives (XXV) can be bound to a solid support and the Suzuki couplings can be carried out on solid support (see XXVIII) as illustrated in Scheme 8. Towards that end treatment of indoline (XXV) with TFA in CH_2Cl_2 , to remove the Boc protecting group, followed extraction from aqueous base provides the free amine (XXXVII). The free amine can be loaded onto a suitable solid support such as (XXVIII) using conditions

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well known to those skilled in the art. Thus, p-nitrophenylchloroformate Wang resin (XXVIII) which can be obtained commercially from sources such as Novabiochem, Inc. is swollen in a suitable solvent such as N-methyl pyrrolidinone and treated with 1.5 equiv. of amine to afford the functionalized resin (XXIX). Suzuki couplings are then carried out in array format by treatment of resins (XXIX) with a suitable palladium source such as Pd(PPh₃)₄ or Pd(dppf)Cl₂ and a suitable base such as 2M aqueous K₂CO₃ or Na₂CO₃ or triethylamine with an excess (typically 5 equivalents) of an aryl boronic acid (procedures for solid-phase Suzuki and other palladium couplings are well-known by those in the art, see for instance L.A. Thompson and J.A. Ellman, *Chem. Rev.* 1996, 96, (1), 555-600). The coupling may be repeated to ensure complete conversion to the desired coupled product. Cleavage from the solid support by treatment with TFA affords the corresponding indoles and indolines (XXX) as their TFA salts.

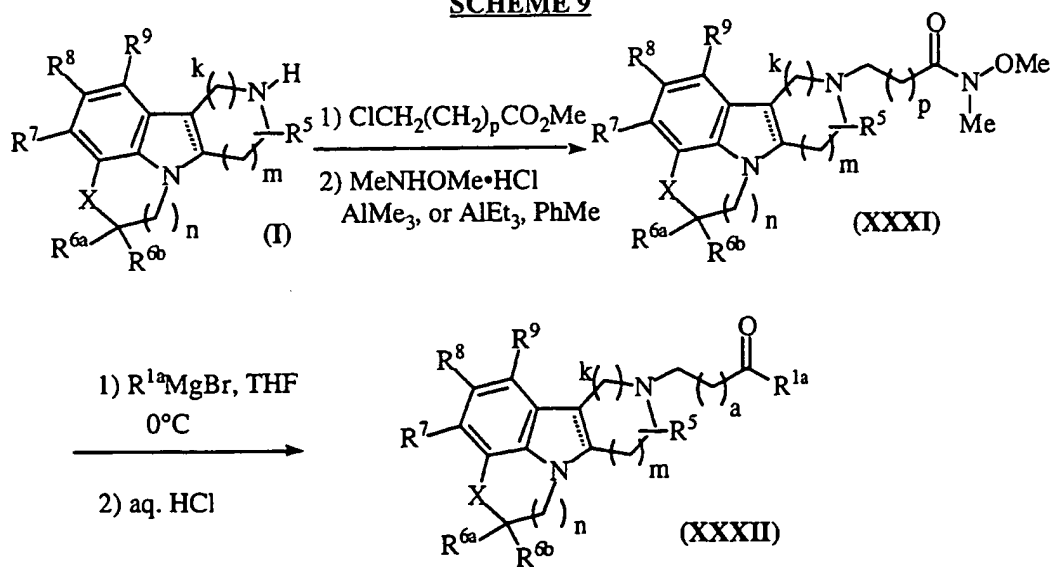
SCHEME 8



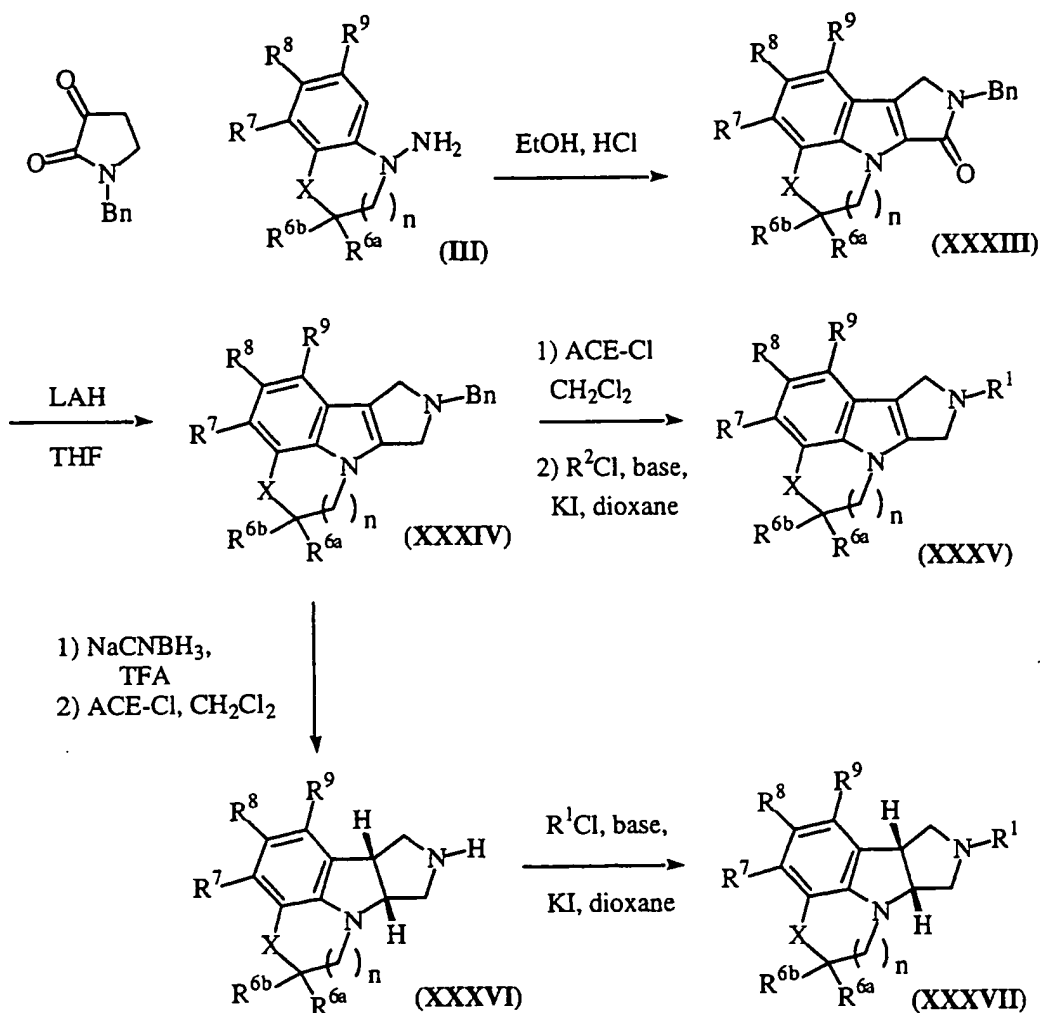
In addition, there exists a wide range of procedures and protocols for functionalizing haloaromatics, arylldiazonium and aryltriflate compounds. These procedures are well known by those in the art and described, for example, by Stanforth, S.P., *Tetrahedron*, **1998**, 263; Buchwald, S.L., et. al., *J. Am. Chem. Soc.*, **1998**, 9722; Stille, J.K., et. al., *J. Am. Chem. Soc.*, **1984**, 7500. Among these procedures are biaryl couplings, alkylations, acylations, aminations, and amidations. The power of palladium catalyzed functionalization of aromatic cores has been explored in depth in the last decade. An excellent review of this field can be found in J. Tsuji, "Palladium Reagents and Catalysts, Innovations in Organic Synthesis", J. Wiley and Sons, New York, **1995**.

One such method to prepare compounds of Formula (I) with substituted R^1 sidechains in a more direct manner is shown in Scheme 9. Alkylation of the indole or indoline derivatives (I, $R^1 = H$) with a haloalkyl ester, such as $ClCH_2(CH_2)_pCO_2Me$, in the presence of NaI or KI and a base such as K_2CO_3 , Na_2CO_3 or the like, in dioxane or THF or other such solvent while heating (see Glennon, R.A., et. al., *Med. Chem. Res.*, **1996**, 197) affords the R^1 alkylated esters. Subsequent formation of the activated amides (XXXI) is accomplished by treatment of the ester with N,O-dimethylhydroxylamine hydrochloride and a Lewis acid such as trimethylaluminum or triethylaluminum in toluene (see, for example, Golec, J.M.C., et. al., *Tetrahedron*, **1994**, 809) at $0^\circ C$. Treatment of the amide (XXXI) with a variety of organometallic agents, such as Grignard reagents $R^{1a}MgBr$, alkyl and aryl lithium reagents etc. (see Sibi, M.P., et. al., *Tetrahedron Lett.*, **1992**, 1941; and more generally House, H.O., *Modern Synthetic Reactions*, W.A. Benjamin, Inc., Menlo Park, CA., **1972**), in a suitable solvent such as THF, ether, etc. at low temperatures affords the substituted ketones (XXXII).

SCHEME 9



Preparation of compounds of Formula (I) where $m=0$, $k = 1$ is outlined in Scheme 10 and described here. Fischer indole cyclization of the previously described hydrazine (III) with a known protected 2,3-dioxopyrrolidine (Carlson, E.H., et. al., *J. Org. Chem.*, **1956**, 1087) under a variety of typical cyclization conditions affords the tetracyclic indole (XXXIII). The reduction may be accomplished with a variety of reducing agents, for example, LAH, DIBAL, etc., to yield the pyrrole fused indole (XXXIV). This derivative can then be deprotected and subsequently alkylated as described previously (see Greene, T.W., Wuts, P.G.W., "Protective Groups in Organic Synthesis, 2nd Edition", John Wiley and Sons, Inc., New York, **1991**, and Scheme 1), to give the R^1 alkylated indole analogs (XXXV). Alternatively, reduction of the indole to the indoline, as described previously (see Scheme 1), followed by deprotection of the benzyl group to give (XXXVI) and alkylation gives access to the corresponding R^1 alkylated indoline derivatives (XXXVII). All the previously described methods to functionalize the aromatic ring, and to afford derivatives of varying R^1 sidechains are applicable to these cores.

SCHEME 10**EXAMPLES**

- 5 Chemical abbreviations used in the Examples are defined above. The detailed processes for preparing the compounds of Formula (I) are illustrated by the following Examples. It is, however, understood that this invention is not limited to the specific details of these examples.
- 10 The Examples as set forth below are intended to demonstrate the scope of the invention but are not intended to limit the scope of the invention. Proton nuclear magnetic resonance spectra (^1H NMR) were measured in chloroform-d

(CDCl₃) unless otherwise specified and the peaks are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). The coupling patterns are reported as follows: s, singlet; d, doublet; dd, doublet of
5 doublets; t, triplet; q, quartet; m, multiplet; bs, broad singlet; bm, broad multiplet.

EXAMPLE 4

ethyl 1-fluoro-6,7,9,12-tetrahydro-5H-pyrido[4,3-b][1,4]thiazepino[2,3,4-hi]indole-11(10H)-carboxylate

5 Step A:

p-Fluorothiophenol (5 g, 40 mmol) and β -propiolactone (2.8 g, 40 mmol) were dissolved in THF (36 mL of freshly distilled) and then placed in an ice bath. 95% sodium hydride (1g, 42.9 mmol) was added in small portions over 1
10 hour. The reaction was allowed to stir at 0°C for 2 hours, then placed in the freezer overnight. The reaction was quenched with ice chips and then acidified with concentrated hydrogen chloride until a pH of 2. The product was extracted with ethyl acetate (1 x 200 mL) and
15 dichloromethane (2 x 200 mL), dried (sodium sulfate) and concentrated to give 3-[(4-fluorophenyl)sulfanyl]propanoic acid (7.08 g, 89%). ¹H NMR (CDCl₃, 300 MHz): δ 7.42-7.35 (m, 2H), 7.02 (t, 2H, J = 8.6 Hz), 4.35 (t, 1H, J = 6.2 Hz), 3.10 (t, 2H, J = 7.3 MHz), 2.63 (t, 2H, J = 7.3 Hz) ppm.

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Step B:

3-[(4-fluorophenyl)sulfonyl]propanoic acid (3 g, 15 mmol) was dissolved in dichloromethane (30 mL) and cooled to 0°C in an ice bath. Oxalyl chloride (10 mL) was added
25 slowly, dimethyl formamide (1 drop) was added and the reaction mixture was stirred at 0°C for 0.5 hours. At which point the reaction was concentrated under reduced pressure to a residue, then resuspended in dichloromethane and cooled to 0°C in an ice bath, CS₂ (1 mL) was added and AlCl₃
30 (4 g, 15 mmol) was added slowly. The reaction mixture was then allowed to warm to room temperature and stirred overnight. Ice chips and water (250 mL) were added and stirred. Concentrated hydrogen chloride was added until pH of 2, and extracted with dichloromethane (3 x 150 mL).
35 Organics were combined, washed with brine (1 x 100 mL) and

water (1 x 100 mL), dried (sodium sulfate), and concentrated to a yellow solid. The solid was purified by flash column chromatography on 100g silica gel, eluting 10% ethyl acetate in hexanes to give 6-fluoro-2,3-dihydro-4H-1-benzothiopyran-4-one (2.55 g, 93%). ¹H NMR (CDCl₃, 300 MHz): δ 7.80-7.76 (m, 1H), 7.27-7.23 (m, 2H), 7.15-7.09 (m, 1H), 3.23 (t, 2H, J = 6.4 Hz), 2.97 (t, 2H, J = 6.4 Hz) ppm.

10 **Step C:**

6-fluoro-2,3-dihydro-4H-1-benzothiopyran-4-one (100 mg, 0.54 mmol) was dissolved in acetic acid (0.5 mL, 1.1 eq), sodium azide (71.2 mg, 1.1 mmol) was added and mixture was heated to 50°C. Sulfuric acid (0.13 mL, 4.3 eq) was added slowly and stirred at 50°C for 1.5 hours. Ice chips (150 mg) were added and a green solid precipitated, this was filtered, washed with water and dried to give 7-fluoro-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (80 mg, 24%). ¹H NMR (CDCl₃, 300 MHz): δ 7.77 (s-broad, 1H), 7.69 (t, 1H, J = 7.3 Hz), 6.94-6.82 (m, 2H), 3.42 (t, 2H, J = 7 Hz), 2.63 (t, 2H, J = 6.7 Hz) ppm.

Step D:

7-fluoro-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (76 mg, 0.38 mmol) dissolved in toluene (1 mL) and cooled to 0°C in an ice bath. Red-Al (275 mL, 0.91mmol) was added and then the reaction allowed to warm to room temperature. The reaction was heated at reflux for 1.5 hours. 1 N sodium hydroxide was added slowly until pH > 10, this was stirred for 10 minutes, extracted with dichloromethane (3 x 25 mL), washed with water, and dried (sodium sulfate). The concentrated organics were purified by preparative thin layer chromatography on silica gel and eluted with 50% ethyl acetate in hexanes to give 7-fluoro-2,3,4,5-

tetrahydro-1,5-benzothiazepine (30.8 mg, 93%). ^1H NMR (CDCl_3 , 300 MHz): δ 7.32 (t, 1H, $J = 7.5$ Hz), 6.53-6.42 (m, 2H), 4.09 (s-broad, 1H), 3.31-3.27 (m, 2H), 2.83-2.79 (m, 2H), 2.11-2.04 (m, 2H) ppm.

5

Step E:

7-fluoro-2,3,4,5-tetrahydro-1,5-benzothiazepine (423 mg, 2.3 mmol) was dissolved in acetic acid (1.15 mL) at 0°C in an ice bath. 2.7 M aqueous sodium nitrite (1 mL) was added and this was stirred over night. Water was added (100 mL) and extracted with dichloromethane (3 x 50 mL), the organics were combined and concentrated to give 7-fluoro-5-nitroso-2,3,4,5-tetrahydro-1,5-benzothiazepine (449 mg, 92%). ^1H NMR (CDCl_3 , 300 MHz): δ 7.43 (t, 1H, $J = 7.1$ Hz), 7.30 (dd, 1H, $J = 9.1$ Hz, $J = 9.2$ MHz), 7.26-7.00 (m, 1H), 4.18 (t, 2H, $J = 5.8$ Hz), 2.86 (t, 2H, $J = 7.2$ Hz), 2.17-2.04 (m, 2H) ppm.

10
15**Step F:**

7-fluoro-5-nitroso-2,3,4,5-tetrahydro-1,5-benzothiazepine (449 mg, 2.11 mmol) was suspended in THF (1 mL of freshly distilled) and cooled to 0°C in an ice bath. Lithium aluminum hydride (80 mg, 2.11 mmol) was added in a portion-wise fashion. The flask was removed from the ice bath and allowed to warm to room temperature and was stirred for 2 hours. Water (0.08 mL) was added and stirred for 10 minutes. 15% sodium hydroxide (0.08 mL) was added stirred for 10 minutes. Water (0.024 mL) was added and stirred for 10 minutes. The reaction was extracted with dichloromethane (2 x 25 mL). The organics were concentrated to a residue, then taken up in minimal amount of dichloromethane and then hydrogen chloride in ether (1 M) was added until precipitation formed, the precipitate was filtered off to give 7-fluoro-3,4-dihydro-1,5-benzothiazepin-5(2H)-amine (471 mg, 95%). ^1H NMR (CD_3OD , 300

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MHz): δ 7.59 (t, 1H, J = 7.5 Hz), 7.28 (d, 1H, J = 9.9 Hz), 7.00 (t, 1H, J = 8.2 Hz), 3.52 (t, 1H, J = 7.5 Hz), 2.92-2.86 (m, 1H), 2.72-2.70 (m, 2H), 2.40-2.31 (m, 1H), 2.2-2.18 (m, 2H) ppm.

5

Step G:

7-fluoro-3,4-dihydro-1,5-benzothiazepin-5(2H)-amine (470 mg, 2 mmol), 1-carbethoxy-4-piperidone (0.3 mL, 2mmol), and ethanol (11mL) were all combined and heated to reflux overnight. The reaction was concentrated to a residue and purified by flash column chromatography on 20 g of silica, eluting with (1%, 2%, 3%, and 10%) methanol in dichloromethane to give the title compound (115 mg, 54%). ¹H NMR (CDCl₃, 300 MHz): δ 6.84 (t, 1H, J = 6.4 Hz), 6.50 (t, 1H, J = 6 Hz), 4.72 (s-broad, 2H), 4.47 (t, 2H, J = 5.8 Hz), 4.20-4.13 (m, 2H), 3.82 (s-broad, 2H), 3.27 (t, 2H, J = 6.7 Hz), 2.69 (s-broad, 2H), 2.27 (q, 2H, J = 6.1 Hz), 1.36 (t, 3H, J = 6.9 Hz) ppm. Mass Spec (ESI): 335 (base M+H).

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EXAMPLE 196

8-[4-(4-fluorophenyl)-4-oxobutyl]-7,8,9,10-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-2(3H)-one

7,8,9,10-hexahydro-2-oxo-1H-pyrido[3',4':4,5]-pyrrolo[1,2,3-de]quinoxalin-2(3H)-one (108 mg, 0.48 mmol) was dissolved in 1.2 mL of MEK. KI (80 mg, 0.48 mmol) and K₂CO₃ (193 mg, 1.40 mmol), and 4-chloro-4'-fluorobutyrophenone (124 mg, 0.62 mmol) were added. The suspension was refluxed for 48 hrs and then cooled to rt. The suspension was filtered and the residue was washed with CH₂Cl₂ (5mL). The solution was concentrated in vacuo. The residue was purified by column chromatography (10% MeOH-CH₂Cl₂) to afford the title compound (20.1mg, 11%) as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.90-7.94

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(m, 2 H), 7.00-7.05 (m, 3H), 6.84-6.89 (m, 1H), 6.42 (d, 1H, 7.0 Hz), 4.74 (s, 2H), 3.66 (s, 2H), 3.00 (t, 2H, 6.9 Hz), 2.78-2.90 (m, 2H), 2.50-2.77 (m, 4H), 1.90-2.05 (m, 2H) ppm. MS (ESI): 392.2 (base, M+H).

5

EXAMPLE 197

4-((8aS,12aR)-6,7,9,10,12,12a-hexahydro-5H-pyrido[4,3-b][1,4]thiazepino[2,3,4-hi]indol-11(8aH)-yl)-1-(4-methylphenyl)-1-butanone hydrochloride

10

General Procedure A:

To a suspension of (8aS,12aR)-6,7,8a,9,10,11,12,12a-octahydro-5H-pyrido[4,3-b][1,4]thiazepino[2,3,4-hi]indole (0.5 mmol) in 1,4-dioxane (3 mL) was added the
15 corresponding chlorobutyrophenone (0.5 - 1.0 mmol), potassium iodine (100 mg) and potassium carbonate (300 mg). The reaction mixture was heated at reflux for 2 days. The solvent was removed under reduced pressure. The residue was treated with water (50 mL) and extracted with diethyl
20 ether (3 x 50 mL). The ether extract was washed with brine (150 mL), dried over MgSO₄, filtered and concentrated to a residue. The residue was purified by flash column chromatography (Silica gel, CH₂Cl₂:CH₃OH 9:1). The product was dissolved in ether (2 mL) and stirred at 0°C for 10
25 minutes, added 1N HCl in ether (0.5 mL) at 0°C. The white crystalline solid was collected by filtration to give the title compound in 50 - 90 % yield.

General procedure B:

30 To a suspension of (8aS,12aR)-6,7,8a,9,10,11,12,12a-octahydro-5H-ptrido[4,3-b][1,4]thiazepino[2,3,4-hi]indole (0.5 mmol) in 1,4-dioxane (3 mL) was added the corresponding alkyl halide (0.5 - 1.0 mmol), potassium iodine (100 mg) and triethylamine (1.5 mmol). The reaction mixture was
35 heated at reflux for 2 days. The solvent was removed under

reduced pressure. The residue was treated with water (50 mL) and extracted with diethyl ether (3 x 50 mL). The ether extract was washed with brine (150 mL), dried over MgSO_4 , filtered and concentrated to a residue. The residue was purified by flash column chromatography (Silica gel, $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$ 9:1). The product was dissolved in ether (2 mL) and stirred at 0°C for 10 minutes, added 1N HCl in ether (0.5 mL) at 0°C . The white crystalline solid was collected by filtration to give the title compound in 50 - 90 % yield.

The title compound was prepared from addition of 4-chloro-4'-methylbutyrophenone to (8aS,12aR)-6,7,8a,9,10,11,12,12a-octahydro-5H-pyrido[4,3-b][1,4]thiazepino[2,3,4-hi]indole following General procedure A above. ^1H NMR (300 MHz, CDCl_3) δ 7.86 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 7.7 Hz, 1H), 6.84 (d, J = 7.3 Hz, 1H), 6.61 (dd, J = 7.7 Hz, 7.3 Hz, 1H), 3.72 - 3.86 (m, 2H), 3.44 - 3.59 (m, 2H), 3.22 - 3.27 (m, 1H), 2.98 - 3.14 (m, 7H), 2.41 (s, 3H), 2.68 - 2.84 (m, 2H), 1.89 - 2.16 (m, 6H) ppm. MS - ESI: 407 $[\text{MH}]^+$

EXAMPLE 203

(8aS,12aR)-11-[3-(4-fluorophenoxy)propyl]-6,7,8a,9,10,11,12,12a-octahydro-5H-pyrido[4,3-b][1,4]thiazepino[2,3,4-hi]indole hydrochloride

The title compound was prepared from addition of 3-chloro-1-(4-fluorophenoxy)propane to (8aS,12aR)-6,7,8a,9,10,11,12,12a-octahydro-5H-pyrido[4,3-b][1,4]thiazepino[2,3,4-hi]indole following General procedure A of Example 197. ^1H NMR (300 MHz, CDCl_3) δ 6.91-7.00 (m, 3H), 6.79-6.87 (m, 3H), 6.62 (dd, J = 7.7 Hz, 7.3 Hz, 1H), 3.97 (t, J = 6.2, 2H), 3.70 - 3.87 (m, 1H), 3.50-3.60 (m, 1H), 3.18 - 3.31 (m, 2H), 2.90 - 3.12 (m, 2H),

2.70 - 2.80 (m, 2H), 2.40-2.62 (m, 2H), 2.22 - 2.38 (m, 1H), 1.90 - 2.11 (m, 7H) ppm. MS - ESI: 399 [MH]⁺

EXAMPLE 210

5 4-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-pyridinyl)-1-butanone hydrochloride

The title compound was prepared from addition of the
10 of 4-chloro-1-(4-pyridyl)butan-1-one to 3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline following General procedure A of Example 197. ¹H NMR (300 MHz, CDCl₃) δ 8.79 (dd, J = 4.4 Hz, 1.8 Hz, 2H), 7.74 (dd, J =
15 4.4 Hz, 1.4 Hz, 2H), 6.64 (dd, J = 7.4 Hz, 7.6 Hz, 1H), 6.49 (d, J = 6.9 Hz, 1H), 6.39 (d, J = 7.7 Hz, 1H), 3.54 -3.62 (m, 1H), 3.23 - 3.31 (m, 2H), 3.13 - 3.17 (m, 1H), 2.95 - 3.03 (m, 2H), 2.85 (s, 3H), 2.76 - 2.84 (m, 2H), 2.57 - 2.60 (m, 1H), 2.31 - 2.41 (m, 1H), 2.22 (td, J = 11.7 Hz,
20 2.9 Hz, 1H), 1.92 - 2.02 (m, 3H), 1.83 - 1.88 (m, 1H), 1.66 - 1.76 (m, 2H) ppm. MS (CI, NH₃) m/e 376 (base, M+H⁺).

The title compound was separated into the corresponding enantiomers by chiral chromatographic separation. (Chiralpak AD column, methanol/ethanol :
25 50/50): ¹H NMR (300 MHz, CDCl₃) δ 8.79 (dd, J = 4.4 Hz, 1.8 Hz, 2H), 7.74 (dd, J = 4.4 Hz, 1.4 Hz, 2H), 6.64 (dd, J = 7.4 Hz, 7.6 Hz, 1H), 6.49 (d, J = 6.9 Hz, 1H), 6.39 (d, J = 7.7 Hz, 1H), 3.54 -3.62 (m, 1H), 3.23 - 3.31 (m, 2H), 3.13 - 3.17 (m, 1H), 2.95 - 3.03 (m, 2H), 2.85 (s, 3H), 2.76 -
30 2.84 (m, 2H), 2.57 - 2.60 (m, 1H), 2.31 - 2.41 (m, 1H), 2.22 (td, J = 11.7 Hz, 2.9 Hz, 1H), 1.92 - 2.02 (m, 3H), 1.83 - 1.88 (m, 1H), 1.66 - 1.76 (m, 2H) ppm. MS (CI, NH₃) m/e 376 (base, M+H⁺).

EXAMPLE 211

(6bR,10aS)-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline

5 Step A:

The procedure described in Example 4, Steps E through G, was utilized to prepare ethyl-2-oxo-2,3,9,10-tetrahydro-1H-pyrido[3',4':4,5]-pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate from the corresponding amine, 1,3,4-trihydroquinoxalin-2-one, and ethyl 4-oxopiperidinecarboxylate. This indole (5.74 g, 19.2 mmol) was dissolved in TFA (100 mL). The reaction was cooled to 0°C. NaCNBH₃ (3.96 g, 63.0 mmol) was added in small portions over 30 min, keeping the temperature less than 5°C. The reaction was stirred at r.t. for 4 hr. Ice was added to the reaction flask, and the reaction was basified with 50% NaOH until pH=12. Water (80mL) was added to dissolve the precipitate. The reaction was extracted with CHCl₃ (3 x 200 mL). The combined organic layers were washed with brine, dried, and concentrated to afford ethyl (6bR,10aS)-2-oxo-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (4.41 g, 77%). ¹H NMR (CDCl₃, 300 MHz) δ 8.45 (bs, 1H), 6.86 (d, J = 7.4 Hz, 1H), 6.74 (dd, J = 7.7 Hz, 7.7 Hz, 1H), 6.63 (d, J = 7.3 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 3.89-3.993 (m, 2H), 3.41-3.47 (m, 2H), 3.33-3.41 (m, 2H), 3.12-3.31 (m, 1H), 2.69-2.75 (m, 2H), 1.90-1.92 (m, 2H), 1.28 (t, J = 7.3 Hz, 3H) ppm. MS - APcI: 302 [MH]⁺

30 Step B:

To ethyl-(6bR,10aS)-2-oxo-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (4.41 g, 14.6 mmol) was added 1M BH₃ THF complex solution (36.6 mL). The reaction was heated under reflux for 5 hr.. After the reaction cooled down to r.t,

6N HCl (40 mL) was added dropwise with chilling. The reaction solution was heated under reflux for 30 minutes. After cooled down to r.t., 1N NaOH was added to adjust the pH to 8. The reaction was extracted with CH₂Cl₂ (2 x 200 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated to afford ethyl (6bR,10aS)-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (4.10 g, 98%). The product was used in next step without further purification. MS - APcI: 288 [MH]⁺

Step C:

To ethyl (6bR,10aS)-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (4.10 g, 14.3 mmol) was added n-butanol (18.0 mL) and KOH powder (3.0 g). The reaction was heated at 119 °C in a sealed tube for 18 hr.. The solvent was removed under reduced pressure. To the residue was added water (30 mL) extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated to afford the title compound as a pale yellow oil (2.70 g, 78%). MS - ESI: 216 [MH]⁺

EXAMPLE 212

4-((6bR,10aS)-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone

Step A:

To 2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline (2.70 g, 10.8 mmol) was added 1N NaOH (40.0 mL) and dioxane (40.0 mL). Boc₂O was added in small portions in 30 minute at 0 °C. The reaction was stirred at r.t. for 18 hr.. The reaction was extracted with CH₂Cl₂ (3 x 150 mL). The combined organic

layers were washed with brine, dried over MgSO_4 , and concentrated to afford a residue which was purified by flash column chromatography (Hexane/Ethyl acetate: 50/50) to afford tert-butyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate. The racemate could be separated by Chiralcel OD column (5cm x 50 cm, 20u; IPA/Hexane: 8%) to afford the corresponding enantiomers.

10 **Step B:**

To either of the enantiomers of tert-butyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (790 mg, 2.25 mmol) were added 20% TFA/ CH_2Cl_2 (5 mL), stirred at r.t. overnight. The solution was concentrated to a residue to afford the TFA salt in 99% yield. To this indoline TFA salt (493.5 mg, 1.5 mmol) was added triethylamine (0.4 mL), K_2CO_3 (300 mg) KI (100 mg) and 1,4-dioxane (6 mL). 4-Chloro-4'-fluorobutyrophenone (3.37 mmol) was then added and the mixture was heated at 103°C in a sealed tube for 24 hr.. The solvent was removed under reduced pressure. To the residue was added water (30 mL) extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated to a residue. The residue was purified by flash column chromatography to afford the title compound (280 mg, 53% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 7.97 - 8.02 (m, 2H), 7.09 - 7.15 (m, 2H), 6.51 - 6.61 (m, 2H), 6.38 (dd, $J = 7.3$ Hz, $J = 1.4$ Hz, 1H), 3.64 - 3.72 (m, 2H), 3.26 - 3.49 (m, 2H), 3.13 - 3.24 (m, 2H), 2.99 - 3.04 (m, 2H), 2.91 - 2.97 (m, 1H), 2.61 - 2.79 (m, 2H), 2.43 - 2.53 (m, 2H), 2.34 - 2.43 (m, 1H), 1.95 - 2.13 (m, 4H) ppm. MS - ESI: 380 $[\text{MH}]^+$

EXAMPLE 217

(6bR,10aS)-8-[3-(6-fluoro-1,2-benzisoxazol-3-yl)propyl]-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline hydrochloride

5

Step A:

To a cold boron trifluoride etherate (280 mmol) solution was added 3-fluorophenol or phenol (89 mmol) and 4-chlorobutyryl chloride (178 mmol). The resulting
10 solution was stirred at 130°C for 18 hours. The reaction mixture was cooled and poured into ice water (100 mL). After stirring for 10 minutes, the water mixture was extracted with ether (3 x 100 mL). The ether layer was washed with brine (100 mL), dried over MgSO₄, filtered and
15 concentrated to a residue to afford 4-chloro-1-(4-fluoro-2-hydroxyphenyl)butan-1-one and 4-chloro-1-(2-hydroxyphenyl)butan-1-one in 52% - 67% yield, which was used in the following step without further purification.

20 **Step B:**

To pyridine (25 mL) was added the corresponding ketone from Step A (46.5 mmol) and hydroxylamine hydrochloride (53.5 mmol). The resultant mixture was stirred at ambient temperature overnight and then poured into dilute HCl (100
25 mL). The mixture was stirred for 5 minutes and extracted with ether (3 x 50 mL). The ether layer was dried over MgSO₄, filtered and concentrated to a residue to afford (1E)-4-chloro-1-(4-fluoro-2-hydroxyphenyl)-1-butanone oxime and (1E)-4-chloro-1-(2-hydroxyphenyl)-1-butanone oxime in
30 99% yield, which were used in the following step without further purification.

Step C:

To acetic anhydride (10 mL) was added the
35 corresponding oxime from Step B (40.0 mmol). The reaction mixture was heated at 60°C for 2 hours, then poured into

ether (10 mL). The mixture was washed with sat. NaHCO_3 solution (4 x 10 mL), then with brine (10 mL). The organic layer was separated, dried over MgSO_4 , filtered and concentrated to afford 2-[(1E)-N-(acetyloxy)-4-chlorobutanimidoyl]-5-fluorophenyl acetate and 2-[(1E)-N-(acetyloxy)-4-chlorobutanimidoyl]phenyl acetate in 61% - 75% yield.

Step D:

To the corresponding bis-acylated derivatives from Step C (5.2 mmol) in ethanol (4 mL) was added KOH (14.4 mmol). The reaction mixture was refluxed for 2 hours, cooled down to rt, added ethyl acetate (10 mL), washed with brine (10 mL), dried over MgSO_4 , filtered and concentrated to a residue. The residue was purified by silica gel flash column chromatography (Ethyl acetate/ Hexane: 3:7) to afford 3-(3-chloropropyl)-6-fluoro-1,2-benzisoxazole and 3-(3-chloropropyl)-1,2-benzisoxazole in 32% yield.

Step E:

The title compound was prepared from addition of 3-(3-chloropropyl)-6-fluoro-1,2-benzisoxazole from Step D and (6bR,10aS)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline following General procedure A, Example 197. ^1H NMR (300 MHz, CDCl_3) δ 7.63 (dd, $J = 8.8$ Hz, 4.7 Hz, 1H), 7.20 - 7.24 (m, 1H), 7.03 - 7.10 (m, 1H), 6.65 (dd, $J = 7.7$ Hz, 7.7 Hz, 1H), 6.50 (d, $J = 7.3$ Hz, 1H), 6.41 (d, $J = 7.3$ Hz), 3.73 - 3.77 (m, 1H), 3.55 - 3.62 (m, 1H), 3.21 - 3.32 (m, 3H), 2.91 - 3.10 (m, 3H), 2.86 (s, 3H), 2.75 - 2.82 (m, 2H), 2.54 - 2.63 (m, 1H), 2.41 - 2.48 (m, 1H), 1.95 - 2.11 (m, 6H) ppm. MS (CI, NH_3) m/e 407 (base, $\text{M}+\text{H}^+$).

EXAMPLE 218

(6bR,10aS)-8-[3-(1,2-benzisoxazol-3-yl)propyl]-3-methyl-
2,3,6b,7,8,9,10,10a-octahydro-1H-
pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline hydrochloride

5

The title compound was prepared from addition 3-(3-chloropropyl)-1,2-benzisoxazole from Step D Example 22 and (6bR,10aS)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline following the
10 General procedure A of Example 197. ¹H NMR (300 MHz, CDCl₃) δ 7.59 -7.62 (m, 1H), 7.46 - 7.50 (m, 2H), 7.20 - 7.25 (m, 1H), 6.57 (dd, J = 7.7 Hz, 7.3 Hz, 1H), 6.43 (d, J = 6.9 Hz, 1H), 6.33 (d, J = 7.3 Hz), 3.48 - 3.52 (m, 1H), 3.06 - 3.25 (m, 4H), 2.94 - 2.99 (m, 2H), 2.70 - 2.89 (m,
15 4H), 2.79 (s, 3H), 2.20 - 2.65 (m, 3H), 1.92 - 2.07 (m, 4H) ppm. MS (CI, NH₃) m/e 389 (base, M+H⁺).

EXAMPLE 255

(6bR,10aS)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-
20 pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline

The procedure described in Example 4, Steps E through G, was utilized to prepare ethyl 2,3,9,10-tetrahydro-2-oxo-1H-pyrido[3',4':4,5]-pyrrolo[1,2,3-de]quinoxaline-8(7H)-
25 carboxylate from the corresponding amine, 1,3,4-trihydroquinoxalin-2-one, and ethyl 4-oxopiperidinecarboxylate

Step A:

30 Sodium cyanoborohydride (4.0 g, 65 mmol) was added, in small portions, to a vigorously stirred solution of ethyl 2,3,9,10-tetrahydro-2-oxo-1H-pyrido[3',4':4,5]-pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (11.97 g, 40 mmol) in trifluoroacetic acid (125 mL) cooled in an ice-
35 water bath, under nitrogen. After the addition was

complete, the mixture was stirred for 30 min and then poured slowly into ammonium hydroxide (300 mL) containing ice followed by the addition of enough 1N sodium hydroxide to make the mixture basic. The mixture was extracted with dichloromethane (2X) and the extract was washed with water, dried over magnesium sulfate, and evaporated to dryness to yield 10.89 g (90%) of ethyl (6bR,10aS)-2-oxo-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate as an off-white powder, m.p. 167-168°C (dec., sinters at 70°C). ¹H NMR (CDCl₃, 300 MHz) δ 1.28 (t, J = 7 Hz, 3H), 1.81-1.95 (m, 2H), 3.13-3.22 (m, 1H), 3.23-3.39 (m, 1H), 3.44 (d, J = 14.7 Hz, 1H), 3.41-3.51 (m, 1H), 3.80-3.95 (m, 1H), 3.98 (d, J = 14.7 Hz, 2H), 4.16 (q, 2H), 6.59 (d, J = 7.7 Hz, 1H), 6.74 (t, J = 7.7 Hz, 1H), 6.83 (d, J = 7.7 Hz, 1H), 8.17 (s, 1H) ppm. MS (CI): 302 (M+H⁺).

Step B:

Sodium hydride (900 mg of 60% dispersion in oil; 22.5 mmol) was washed with hexane, and suspended in anhydrous dimethylformamide (5 mL). The suspension was added to a stirred solution of ethyl (6bR, 10aS)-2-oxo-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (6.02 g, 20 mmol) in anhydrous dimethylformamide (50 mL) under nitrogen. After gas evolution had subsided, the mixture was cooled in ice-water bath and treated with iodomethane (3.55 g., 25 mmol). The mixture was stirred at room temperature for 1 h and then concentrated. The residue was treated with water and extracted with dichloromethane (2X) and the extract was washed with brine, dried over magnesium sulfate and evaporated to dryness to yield 5.48 g (87%) of ethyl (6bR,10aS)-3-methyl-2-oxo-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-

carboxylate as a tan solid, m.p. 149-151°C (dec.). [M+H]
calc. 316; found 316. ¹H NMR (CDCl₃, 300MHz) δ 1.28 (t, J =
7.3 Hz, 3H), 1.85 to 1.93 (m, 1H), 2.65 to 2.82 (m, 1H), 3.08
to 3.25 (m, 1H), 3.25 to 3.40 (m, 1H), 3.30 - 3.50 (m, 1H),
5 3.34 (s, 3H), 3.42 (d, J = 14.3 Hz, 1H), 3.85 to 4.0
(m, 1H), 4.02 (d, J = 14.3 Hz, 1H), 4.15 (q, J = 7.2 Hz, 4H),
6.76 (d, J = 8.1 Hz, 1H), 6.83 (t, J = 7.3 Hz, 1H), 6.90
(d, J = 7.3 Hz, 1H). MS (CI): 316 (M+H⁺).

10 **Step C:**

A solution of borane in tetrahydrofuran (1M, 33 mL, 33
mmol) was added dropwise to a stirred solution of ethyl
(6bR, 10aS)-3-methyl-2-oxo-2,3,6b,9,10,10a-hexahydro-1H-
pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-
15 carboxylate (5.24 g, 16.6 mmol) in anhydrous
tetrahydrofuran (25 mL) under nitrogen. After the addition
was complete, the mixture was stirred and heated at reflux
for 1 h, cooled and treated with 6N hydrochloric acid (15
mL). It was then heated under reflux for 30 min, cooled
20 and evaporated to dryness under reduced pressure. The
residue was dissolved in a minimum quantity of water and
the solution basified with 1N sodium hydroxide and
extracted with dichloromethane (2X). The extract was
washed with water, dried over magnesium sulfate, and
25 concentrated to yield 4.65 g (93%) of ethyl (6bR,10aS)-3-
methyl-2,3,6b,9,10,10a-hexahydro-1H-
pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-
carboxylate as a viscous liquid. ¹H NMR (CDCl₃, 300 MHz) δ
1.28 (t, J = 7 Hz, 3H), 1.68-1.78 (m, 1H), 1.78-1.93 (m,
30 2H), 2.81-2.90 (m, 2H), 2.86 (s, 3H), 3.05-3.26 (m, 2H),
3.26-3.38 (m, 2H), 3.56-3.75 (m, 2H), 3.79-3.87 (m, 1H),
4.16 (q, J = 7 Hz, 2H), 6.41 (d, J = 8.1 Hz, 1H), 6.61 (d,
J = 8.1 Hz, 1H), 6.67 (t, J = 8.1 Hz, 1H) ppm. MS (CI):
302 (M+H⁺).

Step D:

Powdered potassium hydroxide (10.0 g) was added to a stirred solution of ethyl (6bR, 10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (4.52 g, 15.0 mmol) in warm 1-butanol (50 mL) and the resulting mixture was heated under reflux for 5h. It was then evaporated under reduced pressure and the residue treated with water and extracted with dichloromethane (2X). The extract was washed with water, dried over magnesium sulfate and concentrated to yield 3.27 g (95%) of the title compound as a viscous liquid. ¹H NMR (CDCl₃, 300 MHz) δ 1.74-1.93 (m, 4H), 2.57-2.71 (m, 1H), 2.80-2.95 (m, 3H), 2.87 (s, 3H), 2.95-3.12 (m, 2H), 3.26-3.38 (m, 3H), 3.55-3.64 (m, 1H), 6.41 (d, J = 7.3 Hz, 1H), 6.51 (d, J = 7.3 Hz, 1H), 6.65 (t, J = 7.3 Hz, 1H) ppm. MS (CI): 230 (M+H⁺).

EXAMPLE 256

(6bR,10aS)-3-ethyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline

Utilizing the material from Example 255 Step A, the title compound was prepared in analogous fashion using ethyl iodide as the alkyl halide and following the procedure of Step B-D of Example 255, as a light brown amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 1.15 (t, 3H), 1.70-2.01 (m, 3H), 2.65-2.70 (t, J = 9.6 Hz, 3H), 2.70-2.95 (m, 2H), 2.95-3.13 (m, 2H), 3.13-3.72 (m, 5H), 3.60-3.95 (m, 1H), 6.39 (d, J = 8.0 Hz, 1H), 6.47 (d, J = 7.4 Hz, 1H), 6.64 (t, J = 7.3 Hz, 1H) ppm. MS (CI): 244 (M+H⁺).

Step B:

Ethyl (6bR,10aS)-3-ethyl-2-oxo-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-

de]quinoxaline-8(7H)-carboxylate. Viscous brown liquid.
Yield 70%. MS (CI) 330 (M+H⁺).

Step C:

5 Ethyl (6bR,10aS)-3-ethyl-2,3,6b,9,10,10a-hexahydro-1H-
pyrido[3',4':4,5]pyrrolol[1,2,3-de]quinoxaline-8(7H)-
carboxylate. Viscous brown liquid. Yield 70%. MS (CI):
316 (M+H⁺).

10 **EXAMPLE 257**

(6bR,10aS)-3-propyl-2,3,6b,7,8,9,10,10a-octahydro-1H-
pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline

Step A:

15 Utilizing the material from Example 255 Step A, the
title compound was prepared in analogous fashion using
propyl iodide as the alkyl halide and following the
procedure of Step B-D of Example 255, as an amorphous tan
solid. ¹H NMR (CDCl₃, 300 MHz) δ 0.94 (t, 2H), 1.40-2.01
20 (m, 6H), 2.65-2.70 (t, J = 9.6 Hz, 2H), 2.70-2.95 (m, 2H),
2.95-3.45 (m, 7H), 3.3.60-3.95 (m, 1H), 6.37(d, J = 7.7
Hz, 1H), 6.46 (d, J = 7.0 Hz, 1H), 6.64 (t, J = 7.6 Hz)
ppm. MS (CI): 258 (M+H⁺).

25 **Step B:**

Ethyl (6bR,10aS)-3-propyl-2-oxo-2,3,6b,9,10,10a-
hexahydro-1H-pyrido[3',4':4,5]pyrrolol[1,2,3-
de]quinoxaline-8(7H)-carboxylate. Viscous brown liquid.
Yield 72%. MS (CI) 344 (M+H⁺).

30

Step C:

Ethyl (6bR,10aS)-3-propyl-2,3,6b,9,10,10a-hexahydro-
1H-pyrido[3',4':4,5]pyrrolol[1,2,3-de]quinoxaline-8(7H)-
carboxylate. Light brown viscous liquid. Yield 69%. MS
35 (CI): 330 (M+H⁺).

EXAMPLE 258

(6bR,10aS)-3-isopropyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline

5

Step A:

Utilizing the material from Example 255 Step A, the title compound was prepared in analogous fashion using isopropyl iodide as the alkyl halide and following the procedure of Step B-D of Example 255, as a viscous brown liquid. ¹H NMR (CDCl₃, 300 MHz) δ 1.18 (d, 6H), 1.60-1.67 (m, 1H), 1.71-1.94 (m, 2H), 2.63- 2.75 (m, 2H), 2.81-2.95 (m, 2H), 2.99-3.20 (m, 2H), 3.30-3.55 (m, 3H), 3.99-4.12 (m, 1H), 6.45 (d, J = 7.4 Hz, 2H), 6.65 (t, J = 7.3 Hz, 1H) ppm. MS (CI): 258 (M+H⁺).

15

Step B:

Ethyl (6bR,10aS)-3-isopropyl-2-oxo-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate. Viscous brown liquid. Yield 69%. MS (CI) 344 (M+H⁺).

20

Step C:

Ethyl (6bR,10aS)-3-isopropyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate. Viscous brown liquid. Yield 97%. MS (CI): 330 (M+H⁺).

25

EXAMPLE 259

(6bR,10aS)-3-butyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline

30

Step A:

Utilizing the material from Example 255 Step A, the title compound was prepared in analogous fashion using n-

35

butyl iodide as the alkyl halide and following the procedure of Step B-D of Example 255, as a viscous brown liquid. ^1H NMR (CDCl_3 , 300 Mhz) δ 0.95 (t, 3H), 1.30-1.45 (m, 2H), 1.50-1.65 (m, 2H), 1.95-2.15 (m, 2H), 2.65-2.80 (m, 2H), 2.65-2.80 (m, 2H), 2.85-3.08 (m, 1H), 3.08-3.22 (m, 3H), 3.22-3.40 (m, 6H), 3.68-3.78 (m, 1H), 6.38 (d, J = 7.1 Hz), 6.46 (d, J = 7.1 Hz, 1H), 6.66 (t, J = 7.7 Hz, 1H) ppm. MS (CI): 436 ($\text{M}+\text{H}^+$).

10 **Step B:**

Ethyl (6bR,10aS)-3-butyl-2-oxo-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolol[1,2,3-de]quinoxaline-8(7H)-carboxylate. Viscous brown liquid. Yield 82%. MS(CI): 358 ($\text{M}+\text{H}^+$).

15

Step C:

Ethyl (6bR,10aS)-3-butyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolol[1,2,3-de]quinoxaline-8(7H)-carboxylate. Viscous brown liquid. Yield 92%. MS (CI): 344 ($\text{M}+\text{H}^+$).

20

EXAMPLE 260

(6bR,10aS)-3-benzyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline

25

Step A:

Utilizing the material from Example 255 Step A, the title compound was prepared in analogous fashion using benzyl iodide as the alkyl halide and following the procedure of Step B-D of Example 255, as a viscous liquid. ^1H NMR(CDCl_3 , 300 MHz) δ 1.60-2.0 (m, 2H), 2.55-2.95(m, 4H), 2.95-3.15 (m, 2H), 3.20-3.45 (m, 3H), 4.40 (q, J = 16.1 Hz, 2H), 6.41 (d, J = 7.1 Hz, 1H), 6.51 (d, J = 7.1 Hz, 1H), 6.62 (t, J = 7.1 Hz, 1H), 7.20-7.40 (m, 5H) ppm. MS (CI): 306 ($\text{M}+\text{H}^+$).

35

Step B:

Ethyl (6bR,10aS)-3-benzyl-2-oxo-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolol[1,2,3-de]quinoxaline-8(7H)-carboxylate. Viscous brown liquid.
5 Yield 80%. MS (CI) 392 (M+H⁺).

Step C:

Ethyl (6bR,10aS)-3-benzyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolol[1,2,3-de]quinoxaline-8(7H)-carboxylate. Viscous brown liquid. Yield 85%. MS (CI):
10 378 (M+H⁺).

EXAMPLE 261

4-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone
15

A mixture of 3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline (3.20 g, 14 mmol), 4-chloro-4'-fluoro-butyrophenone (4.21 g, 21 mmol), triethylamine (3 mL), potassium iodide (3.48 g, 21 mmol), dioxane (25 mL), and toluene (25 mL) was stirred and refluxed for 15 h under an atmosphere of nitrogen and then
20 evaporated under reduced pressure to remove the volatiles. The residue was triturated with a small volume of dichloromethane and decanted from the insoluble material. The process was repeated two more times and the combined dichloromethane solutions was added to 0.5N solution of
25 hydrogen chloride in ether (200 mL). The salt that separated was filtered off, washed with ether, dissolved immediately in a minimum quantity of water and the solution extracted with ether. The ether extract was discarded and aqueous layer basified with 10% aqueous sodium hydroxide.
30 The resulting mixture was extracted with dichloromethane (2X) and the extract dried over magnesium sulfate and
35

stripped of the solvent under reduced pressure to yield 4.15 g (75%) of a highly viscous brown liquid. ^1H NMR (CDCl_3 , 300 MHz) δ 1.79-2.13 (m, 6H), 2.21-2.32 (m, 1H), 2.32-2.44 (m, 2H), 2.60-2.71 (m, 1H), 2.75-2.92 (m, 2H), 2.86 (s, 3H), 2.98 (t, $J = 7.3\text{Hz}$, 2H), 3.04-3.16 (m, 1H), 3.16-3.35 (m, 2H), 3.55-3.64 (m, 1H), 6.39 (d, $J = 8.1\text{ Hz}$, 1H), 6.50 (d, $J = 8.1\text{ Hz}$, 1H), 6.64 (t, $J = 7.7\text{ Hz}$, 1H), 7.12 (t, 2H), 8.01 (m, 2H) ppm. MS (CI): 394 ($\text{M}+\text{H}^+$).

The above compound was resolved into its enantiomers on chiral HPLC column. 4-((6bS,10aR)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone. Viscous tan liquid. $[\alpha]^D = -36.8^\circ$ ($c=0.886$, CHCl_3). MS (CI): 394 ($\text{M}+\text{H}^+$).

4-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone. Viscous tan liquid. $[\alpha]^D = +33.6^\circ$ ($c=0.646$, CHCl_3). MS (CI): 394 ($\text{M}+\text{H}^+$).

20

EXAMPLE 262

4-((6bR,10aS)-3-ethyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone

25

Treatment of (6bR,10aS)-3-ethyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline according to the procedure of Example 261 afforded the title compound in good yield as a viscous brown liquid. ^1H NMR (300 MHz, CDCl_3) δ 1.15 (t, $J = 7.0\text{ Hz}$, 3H), 1.75-2.03 (m, 5H), 2.20 to 2.30 (m, 1H), 2.30-2.42 (m, 2H), 2.63 to 2.77 (m, 3H), 2.77 to 2.87 (m, 1H), 2.98 (t, $J = 7.0\text{ Hz}$, 2H), 3.04-3.43 (m, 5H), 3.64-3.72 (m, 1H), 6.30 (d, $J = 7.7\text{ Hz}$, 1H), 6.47 (d, $J = 7.7\text{ Hz}$, 1H), 6.64 (d, $J = 7.7\text{ Hz}$,

30

1H), 7.12 (t, J = 8.5 Hz, 2H), 7.98 to 8.03 (m, 2H) ppm. MS (CI): 408 (M+H⁺).

EXAMPLE 263

5 4-((6bR,10aS)-3-isopropyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone

Treatment of (6bR,10aS)-3-isopropyl-
10 2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline according to the procedure of Example 261 afforded the title compound in good yield as a viscous, brown liquid. ¹H NMR (CDCl₃, 300 MHz) δ 1.18 (d, J = 6.6 Hz, 6H), 1.82-1.84 (m, 5H), 2.21-
15 2.29 (m, 1H), 2.29-2.41 (m, 2H), 2.64-2.68 (m, 2H), 2.79-2.87 (m, 1H), 2.98 (t, J = 7.3 Hz, 2H), 3.03-3.17 (m, 2H), 3.21-3.45 (m, 3H), 4.03 (dt, J = 6.6, 2.3 Hz, 1H), 6.45 (d, J = 6.2 Hz, 2H), 6.64 (t, J = 7.7 Hz, 1H), 7.12 (t, J = 8.3 Hz, 2H), 8.0-8.03 (m, 2H) ppm. MS(CI): 422 (M+H⁺).
20

EXAMPLE 264

4-((6bR,10aS)-3-benzyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone
25

Treatment of (6bR,10aS)-3-benzyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline according to the procedure of Example 261 afforded the title compound in good yield as a viscous brown liquid.
30 Yield 23%. ¹H NMR (CDCl₃, 300 MHz,) δ 1.84-2.05 (m, 5H), 2.20-2.31 (m, 1H), 2.31-2.43 (m, 2H), 2.64- 2.72 (m, 1H), 2.72-2.80 (m, 1H), 2.80-2.89 (m, 1H), 2.99 (t, J = 7.3 Hz, 2H), 3.06-3.14 (m, 1H), 3.14-3.26 (m, 1H), 3.26-3.34 (m, 2H), 3.65-3.74 (m, 1H), 4.43 (q, J = 16.5 Hz, 2H), 6.40 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 7.0 Hz, 1H),) 6.61 (t, J =
35

8.1 Hz, 1H), 7.13 (t, J = 8.5 Hz, 2H) 7.20-7.35 (m, 5H), 8.00-8.03 (m, 2H) ppm. MS (CI): 470 (M+H⁺).

EXAMPLE 269

5 (6bR,10aS)-8-[3-(4-fluorophenoxy)propyl]-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline

Treatment of (6bR,10aS)-3-methyl-2,3,6b,7,8,9,10,10a-
10 octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline according to the procedure of Example 203 afforded the title compound in good yield as a viscous liquid. Yield 30%. ¹H NMR (CDCl₃, 300 MHz): δ 1.85-2.10 (m, 5H), 2.20-2.40 (m, 1H) 2.40-2.60 (m, 2H), 2.66-2.78 (m, 1H), 2.78-2.95
15 (m, 2H), 2.87 (t, 3H), 3.10-3.35 (m, 4H), 3.55-3.70 (m, 1H), 3.97 (t, J = 6.2 Hz, 2H), 6.40 (d, J = 7.7 Hz, 1H), 6.52 (d, J = 7.3 Hz, 1H), 6.65 (t, J = 7.7 Hz, 1H), 6.79-6.90 (m, 2H), 6.96 (t, J = 8.5 Hz, 2H) ppm. MS (CI): 382 (M+H⁺).

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EXAMPLE 274

(6bR,10aS)-5-(2,4-dichlorophenyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline

25

To a solution of tert-butyl (6bR,10aS)-5-(2,4-dichlorophenyl)-3-methyl-2-oxo-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (100 mg, 0.21 mmol) in THF (5.0 mL), BH₃-THF
30 (1M in THF) (0.82 mL, 0.82 mmol) was added dropwise. After addition was completed, the resulting reaction mixture was refluxed for 4 h, cooled to room temperature, and quenched cautiously with water (1.0 mL). The mixture was evaporated to dryness under reduced pressure and the residue obtained
35 was treated with o-xylene (10 mL) and 1-octene (5 mL) and

heated at reflux for 4 h. The reaction mixture was cooled to room temperature and concentrated to dryness under reduced pressure to give tert-butyl (6bR,10aS)-5-(2,4-dichlorophenyl)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate as a white solid (50 mg, 58%).

The hydrochloride salt of the title compound was prepared from tert-butyl (6bR,10aS)-5-(2,4-dichlorophenyl)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (50 mg) using the deprotection procedures described in Example 275, Step B. The salt formed was free-based with 6 N NaOH to give the title compound (31 mg, 80%).

¹H NMR (CD₃OD, 300 MHz) δ 1.80-1.90 (m, 1H), 1.96-2.10 (m, 1H), 2.50 (m, 2H), 2.76-2.90 (m, 5H), 2.93-3.1 (m, 2H), 3.20-3.50 (m, 4H), 3.50-3.60 (m, 2H), 6.40 (d, 1H), 6.5 (d, 1H), 7.22-7.32 (m, 2H), 7.44 (d, 1H) ppm. MS-CI m/z = 374 [C₂₀H₂₁Cl₂N₃+H]⁺

EXAMPLE 275

(6bR,10aS)-5-(2,4-dichlorophenyl)-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline hydrochloride

Step A:

Typical Procedure for Suzuki Coupling:

The corresponding bromo-indoline (1.0 equiv), the boronic acid (1.5-2 equivs) and barium hydroxide (1.5 equivs) were stirred into a solution of water and DME, then heated at 60 °C while bubbling through a stream of Argon gas for 20 min. The reaction mixture was then cooled to room temperature and Pd(PPh₃)₂Cl₂ (2.5-5 mol%) and PPh₃ (3 equivs based on Pd source) were quickly added and refluxing resumed for 4 hours. When the reaction was completed as shown by TLC,

ethyl acetate was added and the mixture was filtered through a Celite bed. Organic layer was separated, dried over sodium sulfate and concentrated under reduced pressure to a yellow oil. This residue was purified on a flash column eluting with 10% EtOAc/Hexanes to give the desired product.

Tert-butyl (6bR, 10aS)-5-(2,4-dichlorophenyl)-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (37 mg, 60%) was prepared via coupling of tert-butyl (6bR, 10aS)-5-bromo-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (50 mg, 0.13 mmol) with 2,4-dichlorophenyl boronic acid (74 mg, 0.39 mmol) as illustrated above using the general procedure for Suzuki coupling. ¹H NMR (CDCl₃, 300 MHz) δ 1.46 (s, 9H), 1.82-1.96 (m, 2H), 2.74-2.82 (m, 1H), 2.99-3.05 (m, 1H), 3.16-3.22 (m, 2H), 3.33-3.39 (m, 1H), 3.43-3.50 (m, 1H), 3.52-3.57 (m, 1H), 3.62-3.69 (m, 1H), 3.43-3.50 (m, 1H), 3.52-3.57 (m, 1H), 3.62-3.69 (m, 1H), 3.71-3.79 (m, 1H), 3.80-3.85 (m, 1H), 3.89-4.14 (m, 1H), 6.44 (s, 1H), 6.59 (s, 1H), 7.22 (s, 2H), 7.42 (s, 1H) ppm.

Step B:

General procedure for removal of Boc protecting group: The indoline (100-150 mg) is mixed with cold ethanolic hydrochloric acid (4M) (5 mL), and the solution is stirred for 10 min at 0°C. The solvent is removed under reduced pressure and the residue is dissolved in hot acetonitrile with a small amount of methanol. Upon cooling to room temperature, the desired salt is obtained as a crystalline material.

(6bR,10aS)-5-(2,4-dichlorophenyl)-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline hydrochloride (57 mg, 78%) was formed from tert-butyl (6bR,

10aS)-5-(2,4-dichlorophenyl)-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (110 mg) using the deprotection procedure described above to afford the title compound. ¹H NMR

5 (CD₃OD, 300 MHz) δ 1.80-1.92 (m, 1H), 1.96-2.10 (m, 1H), 2.5-2.69 (m, 2H), 2.76-2.90 (m, 2H), 2.97-3.1 (m, 2H), 3.35-3.50 (m, 4H), 3.57-3.70 (m, 2H), 6.40 (d, 1H), 6.5 (d, 1H), 7.22-7.32 (m, 2H), 7.44 (d, 1H) ppm. MS-CI m/z= 361 [C₁₉H₁₉Cl₂N₃+H]⁺

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EXAMPLE 276

4-((6bR,10aS)-5-bromo-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone

15

Typical procedure for alkylation of carbolines:

A mixture of indoline hydrochloride (188 mg, 0.7 mmol) in dioxane (4 mL) was treated with Hunig's base (10 equivs) and heated to reflux for 15 min. To the cooled reaction mixture was added 4-chloro-4'-fluoro-butyrophenone (5 equivs), KI (0.9 equivs), then the whole mixture was refluxed for 48 h. The reaction was then diluted with chloroform (20 mL) and extracted once with saturated solution of ammonium chloride (10 mL) and twice with ice-cold water (100 mL). The organic layer was dried over sodium sulfate and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography eluting with a gradient of hexane/ethylacetate (e.g. 96:4 to 50:50), following with a gradient methanol/dichloromethane (e.g. 1:99 to 3:97) to give the desired product.

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30

The title compound (271 mg, 95%) was obtained from the alkylation of the (6bR,10aS)-5-bromo-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-

pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline hydrochloride (200 mg, 0.65 mmol) with 4-chloro-4'-fluorobutyrophenone (0.53 mL, 3.24 mmol) using the general procedure described above. ¹H NMR (CDCl₃, 300 MHz) δ 2.00-1.30 (m, 4H), 1.82-2.40 (m, 4H), 2.66-2.80 (m, 2H), 2.86 (s, 3H), 3.07-3.37 (m, 4H), 3.55-3.70 (m, 7H), 6.07 (s, 1H), 6.12 (s, 1H), 7.10-7.19 (m, 2H), 7.92-8.10 (m, 2H) ppm. MS -CI/EI m/z = 473 [C₂₄H₂₇BrFN₃O+H]

10

EXAMPLE 277

4-((6bR,10aR)-5-methoxy-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone

15

The title compound (2.0 mg, 52%) was obtained from the alkylation of the optically pure (6bR,10aR)-5-methoxy-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline hydrochloride (4.2 mg) with 4-chloro-4'-fluorobutyrophenone (5.0 equiv)

20

using the general procedure described in Example 276. ¹H NMR (CDCl₃, 300 MHz) δ 1.42-1.79 (m, 4H), 1.92-2.50 (m, 4H), 2.66-2.79 (m, 2H), 2.86 (s, 3H), 3.07-3.32 (m, 4H), 3.55-3.75 (m, 7H), 6.07 (s, 1H), 6.12 (s, 1H), 7.06-7.21 (m, 2H), 7.92-8.10 (m, 2H) ppm. MS -CI/EI m/z = 424

25

[C₂₅H₃₀FN₃O₂+H]

EXAMPLE 278

(8aS,12aR)-2-(2,4-dichlorophenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole hydrochloride

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Step A:

To a solution of tert-butyl 6-nitro-1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indole-2-carboxylate (15.6 g,

49.15 mmol) in ethanol (250 mL) was added a spatula tip of 10% Pd/C. The reaction mixture was shaken under a hydrogen atmosphere (15 psi, Parr apparatus) for 2 h. Upon removal from the Parr apparatus, the reaction mixture was filtered through Celite. The Celite was washed with ethanol and the combined filtrates were concentrated in vacuo to give tert-butyl 6-amino-1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indole-2-carboxylate, quantitatively as a white solid: ¹H NMR (CDCl₃, 500 MHz) δ 1.42-1.67 (m, 9H), 2.74-2.85 (m, 2H), 3.58 (brs, 2H), 3.79 (brs, 2H), 4.60 (brs, 2H), 6.53-6.56 (m, 1H), 6.89-6.99 (m, 2H), 7.77 (brs, 1H) ppm.

Step B:

To a solution of tert-butyl 6-amino-1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indole-2-carboxylate (4.62 g, 16.08 mmol) in benzene (100 mL) was added a catalytic amount of DMAP. An inert atmosphere was created and chloropropionyl chloride (2) (1.68 mL) was added dropwise to the reaction mixture. After stirring at room temperature for 20 min, the reaction mixture was transferred to a separatory funnel containing 50% solution of sodium bicarbonate and was extracted with CH₂Cl₂ (3 x 250 mL). The combined organics were dried over Na₂SO₄ and concentrated in vacuo to give tert-butyl 6-[(3-chloropropanoyl)amino]-1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indole-2-carboxylate as a white solid in 99% yield: ¹H NMR (DMSO, 500 MHz) δ 1.38-1.53 (m, 9H), 2.75-2.99 (m, 2H), 3.65-3.78 (m, 4H), 3.88-3.97 (m, 2H), 4.53 (brs, 2H), 6.88-6.96 (m, 1H), 7.15-7.22 (m, 1H), 7.31-7.37 (m, 1H), 9.72 (brs, 1H), 10.44 (brs, 1H) ppm.

Step C:

To a suspension of NaH (95%) (100 mg, 3.96 mmol) in DMF (4 mL), stirring under an N₂ atmosphere at 0°C, was added dropwise a solution of tert-butyl 6-[(3-

chloropropanoyl)amino]-1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indole-2-carboxylate (500 mg, 1.32 mmol) and TBAI (cat.) in DMF (4 mL). The reaction was heated to 70°C for 6 h then stirred at room temperature for 14 h. The mixture was
5 quenched by slow transfer of the reaction mixture to a separatory funnel containing a saturated solution of sodium bicarbonate. The mixture was extracted with Et₂O (3 x 25 mL). The combined organics were concentrated in vacuo and the resulting residue was recrystallized from CH₃CN to give
10 tert-butyl 5-oxo-4,5,6,7,9,12-hexahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole-11(10H)-carboxylate: ¹H NMR (CDCl₃, 500 MHz) δ 1.49 (brs, 9H), 2.78 (brs, 2H), 3.02-3.07 (m, 2H), 3.84 (brs, 2H), 4.24-4.28 (m, 2H), 4.62 (brs, 2H), 6.66 (d, 1H, J= 7.9 Hz),
15 7.02 (t, 1H, J= 7.9 Hz), 7.19 (d, 1H, J= 7.9 Hz), 7.80 (brs, 1H) ppm.

Step D:

To a solution of tert-butyl 5-oxo-4,5,6,7,9,12-hexahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole-
20 11(10H)-carboxylate (914 mg, 2.68 mmols) in TFA (25 mL) stirring at -20°C was added NaCNBH₃ (675 mg, 10.71 mmols) in 5 portions. The reaction was then stirred at -10°C for 2 h. The yellow reaction solution was quenched by the
25 dropwise addition of 6 N HCl (50 mL) followed by refluxing for 35 min. After cooling to room temperature, the reaction mixture was made basic by slowly pouring it into a solution of K₂CO₃. The mixture was transferred to a separatory funnel and extracted with CH₂Cl₂ (3 x 250 mL).
30 The combined organics were dried over Na₂SO₄ and concentrated in vacuo and purified by column chromatography to give tert-butyl (8aS,12aR)-5-oxo-4,5,6,7,9,10,12,12a-octahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole-11(8aH)-carboxylate. ¹H NMR (CDCl₃, 300 MHz) δ 1.49 (brs,

9H), 1.81-1.94 (m, 2H), 2.77-3.94 (m, 10H), 6.58-6.69 (m, 2H), 6.83 (d, 1H, J= 6.7 Hz), 7.87 (s, 1H) ppm.

Step E:

5 To a solution of tert-butyl (8aS,12aR)-5-oxo-4,5,6,7,9,10,12,12a-octahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole-11(8aH)-carboxylate (449 mg, 1.31 mmols) in DMF (6 mL), stirring under a N₂ atmosphere at -10°C, was added N-bromosuccinimide (243 mg, 1.37 mmols).
10 After 1 h, the brominated compound was precipitated by the addition of crushed ice. The reaction mixture was allowed to warm to room temperature and the solid collected by vacuum filtration. The white solid was washed with H₂O at 0°C and dried under vacuum to give tert-butyl (8aS, 12aR)-
15 2-bromo-5-oxo-4,5,6,7,9,10,12,12a-octahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole-11(8aH)-carboxylate in 65% yield: ¹H NMR (CDCl₃, 500 MHz) δ
1.40-1.53 (m, 9H), 1.80-1.94 (m, 2H), 2.76-2.92 (m, 2H), 3.19-3.89 (m, 8H), 6.71 (s, 1H), 6.93 (s, 1H), 7.35 (brs,
20 1H) ppm.

STEP F :

General lactam reduction procedure: To a solution of the lactam (approx 100 mg) in THF (5.0 mL), BH₃-THF (1M in
25 THF) (4 equivs) is added dropwise. After addition is complete, the resulting reaction mixture is refluxed for 4 h, cooled to room temperature, and quenched cautiously with water (1.0 mL). The mixture is evaporated to dryness under reduced pressure and the residue obtained is treated with
30 o-xylene (10 mL) and 1-octene (5 mL) and heated at reflux for 4 h. The reaction mixture is cooled to room temperature and concentrated to dryness under reduced pressure to give the desired target as a solid.

Tert-butyl (8aS, 12aR)-2-bromo-4,5,6,7,9,10,12,12a-octahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole-
35

11(8aH)-carboxylate (188 mg, 100%) was prepared from the reduction of tert-butyl (8aS, 12aR)-2-bromo-5-oxo-4,5,6,7,9,10,12,12a-octahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole-11(8aH)-carboxylate from Step E (179 mg, 0.82 mmol) using the procedure illustrated above.
¹H NMR (CDCl₃, 500 MHz) δ 0.85-0.95 (m, 2H), 1.30-1.62 (m, 9H), 1.76-2.01 (m, 3H), 2.32-2.46 (m, 1H), 2.77-2.84 (m, 1H), 3.32-3.49 (m, 4H), 3.56-3.98 (m, 3H), 6.64 (s, 1H), 6.72 (s, 1H) ppm.

10

Step G:

Tert-butyl (8aS, 12aR)-2-(2,4-dichlorophenyl)-4,5,6,7,9,10,12,12a-octahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole-11(8aH)-carboxylate (48 mg, 42%) was prepared via coupling of tert-butyl (8aS, 12aR)-2-bromo-4,5,6,7,9,10,12,12a-octahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole-11(8aH)-carboxylate (85 mg, 0.21 mmol) with 2,4-dichlorophenyl boronic acid (60 mg, 0.31 mmol) as illustrated by the general procedure described in Example 275 Step A. This material was used without further purification in the subsequent step.

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tert-butyl (8aS, 12aR)-2-(2,4-dichlorophenyl)-4,5,6,7,9,10,12,12a-octahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole-11(8aH)-carboxylate (35 mg) was deprotected using the procedure described in Example 275 Step B to afford the title compound (20 mg, 63%).

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¹H NMR (DMSO, 500 MHz) δ 1.59-1.76 (m, 1H), 1.79-2.78 (m, 4H), 2.81-5.0 (m, 9H), 6.82-7.20 (m, 2H), 7.32-7.44 (m, 1H), 7.47-7.53 (m, 1H), 7.65-7.75 (m, 1H), 8.81-9.23 (m, 2H) ppm. MS-CI; m/z = 376 [C₂₀H₂₁Cl₂N₃+H]⁺.

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EXAMPLE 279

(8aS, 12aR)-2-(4-methoxy-2-methylphenyl)-4,5,6,7,8a,9,10,11,12,12a-decahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole hydrochloride

35

Tert-butyl (8aS, 12aR)-2-(4-methoxy-2-methylphenyl)-4,5,6,7,9,10,12,12a-octahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole-11(8aH)-carboxylate (48 mg, 52%) was prepared via coupling of the tert-butyl (8aS, 12aR)-2-bromo-4,5,6,7,9,10,12,12a-octahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole-11(8aH)-carboxylate (85 mg, 0.21 mmol) with 2-methyl-4-methoxyphenyl boronic acid (53 mg, 0.31 mmol) using the general procedure described in Example 275 Step A. This material was used without further purification in the subsequent step.

Tert-butyl (8aS, 12aR)-2-(4-methoxy-2-methylphenyl)-4,5,6,7,9,10,12,12a-octahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole-11(8aH)-carboxylate (38 mg) was deprotected using the procedure described in Example 275 Step B to afford the title compound (22 mg, 61%).

¹H NMR (DMSO, 500 MHz) δ 1.86-1.97 (m, 1H), 2.07-2.18 (m, 2H), 2.22 (s, 3H), 2.35-2.48 (m, 2H), 2.62-2.70 (m, 1H), 2.86-2.93 (m, 1H), 3.17-3.71 (m, 9H), 3.79 (s, 3H), 6.71-6.82 (m, 4H), 7.02-7.07 (m, 1H) ppm. MS-CI; m/z = 350[C₂₂H₂₇N₃O+H]⁺.

EXAMPLE 280

(8aS, 12aR)-2-(2,4-dichlorophenyl)-6,7,8a,9,10,11,12,12a-octahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indol-5(4H)-one hydrochloride

Tert-butyl (8aS, 12aR)-2-(2,4-dichlorophenyl)-4-methyl-5-oxo-4,5,6,7,9,10,12,12a-octahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole-11(8aH)-carboxylate (223 mg, 48%) was prepared via coupling of tert-butyl (8aS, 12aR)-2-bromo-4-methyl-5-oxo-4,5,6,7,9,10,12,12a-octahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole-11(8aH)-carboxylate (404 mg, 0.96 mmol) with 2,4-dichlorophenyl boronic acid (275 mg, 1.44

mmol) using the general procedure described in Example 275 Step A.

¹H NMR (CDCl₃, 500 MHz) δ 1.41 (brs, 9H), 1.85-1.98 (m, 2H), 2.83-2.96 (m, 2H), 3.18-3.46 (m, 4H), 3.46-3.54 (m, 2H), 3.76 (d, 1H, J = 1.6 Hz), 3.83 (brs, 1H), 6.63 (s, 1H), 6.92 (s, 1H), 7.18-7.27 (m, 2H), 7.39 (s, 1H), 7.45 (s, 1H) ppm.

Tert-butyl (8aS, 12aR)-2-(2,4-dichlorophenyl)-4-methyl-5-oxo-4,5,6,7,9,10,12,12a-octahydro[1,4]diazepino[3,2,1-hi]pyrido[4,3-b]indole-11(8aH)-carboxylate (75 mg) was deprotected using the procedure described in Example 275 Step B to afford the title compound. (52 mg, 83%)

¹H NMR (CD₃OD, 300 MHz) δ 2.06-2.19 (m, 1H), 2.27-2.36 (m, 1H), 2.80-2.92 (m, 4H), 3.16-3.34 (m, 3H), 3.37-3.59 (m, 4H), 3.68-3.74 (m, 1H), 6.94 (d, 1H, J = 3.3 Hz), 7.04 (d, 1H, J = 3.3 Hz), 7.29-7.38 (m, 2H), 7.53 (d, 1H, J = 1.7 Hz) ppm. MS-Cl; m/z = 389 [C₂₀H₁₉Cl₂N₃O+H]⁺.

20

EXAMPLE 281

(6bS, 11aS)-3-methyl-2,3,7,8,9,10,11,11a-octahydro-1H,6bH-azepino[4',5':4,5]pyrrolo[1,2,3-de]quinoxaline

Step A:

o-Nitrophenyl hydrazine (5.22 g, 34 mmol) and azepin-3-one 2 (5.09 g, 34 mmol) were dissolved in 60 mL of CF₃CH₂OH. The solution was refluxed for 1 hr. The reaction was cooled to rt and concentrated. The organic solid was transferred to a sealed tube, and 100 mL of conc HCl were added. The mixture was heated to 80°C for 18 hrs. The reaction was then cooled to 0°C and ice chips were added to the reaction vessel. The reaction was basified with 50% NaOH until the pH = 14. Dioxane (100 mL) and Boc₂O (8.18 g, 3.7 mmol) were added. This solution was stirred at rt for 18 hrs. The reaction was then concentrated. Brine (50

mL) and CHCl_3 were added to the residue and the biphasic mixture was stirred for 10 min. The layers were separated, and the aqueous phase was re-extracted with CHCl_3 (2 X 30 mL). The combined organic layers were washed with brine, dried, and concentrated to afford 7.8 g of a brown residue. This crude product was purified by column chromatography (1-2% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to afford tert-butyl 7-nitro-1,4,5,6-tetrahydroazepino[4,5-b]indole-3(2H)-carboxylate (5.87 g, 52%) as an amorphous solid. ^1H NMR (CDCl_3 , 300 MHz) δ 9.45 (1H, bs), 8.07 (1H, bd, $J = 8.1$ Hz), 7.7-7.9 (1H, m), 7.13-7.19 (1H, m), 3.69-3.73 (4H, m), 2.9-3.11 (4H, m), 1.50 (9H, s) ppm.

Step B:

NaH was suspended in DMF (2mL) at 0°C . tert-butyl 7-nitro-1,4,5,6-tetrahydroazepino[4,5-b]indole-3(2H)-carboxylate (462 mg, 1.4 mmol) was added as a solution in DMF (4mL) drop-wise. The reaction was heated to 40°C for 10 min was the cooled back to 0°C . Bromoethyl acetate was added drop-wise. The reaction was warmed to rt and stirred for 3 hrs. Brine (20 mL) and EtOAc (20 mL) were added to the reaction and stirred for 10 min. The layers were separated. The aqueous layer was re-extracted with EtOAc (2 X 20 mL). The combined organic layers were washed with brine, dried, and concentrated to afford 498 mg of a brown viscous oil. This crude product was purified by column chromatography (30% EtOAc/hexane) to afford tert-butyl 6-(2-ethoxy-2-oxoethyl)-7-nitro-1,4,5,6-tetrahydroazepino[4,5-b]indole-3(2H)-carboxylate as an orange amorphous solid (453 mg, 53%). ^1H NMR (CDCl_3 , 300 MHz) δ 7.80 (1H, d, $J = 7.7$ Hz), 7.10-7.75 (1H, m), 7.11-7.16 (1H, m), 4.82 (2H, s), 4.25 (2H, q, $J = 7.0$ Hz), 3.6-3.9 (4H, m), 2.8-3.1 (4H, m), 1.48 (9H, s), 1.30 (3H, t, $J = 7.0$ Hz) ppm.

Step C:

Tert-butyl 6-(2-ethoxy-2-oxoethyl)-7-nitro-1,4,5,6-tetrahydroazepino[4,5-b]indole-3(2H)-carboxylate (146 mg, 0.35 mmol) was added to EtOH (15 mL). The reaction flask was evacuated and shaken on a Parr shaker at 55 psi of H₂.

- 5 After 18 hrs, the reaction was disassembled and was filtered over a cake of Celite. The supernatant was concentrated to afford 115 mg of a black material, which was purified by column chromatography. tert-butyl 2-oxo-2,3,7,8,10,11-hexahydro-1H,9H-
- 10 azepino[4'5':4,5]pyrrolo[1,2,3-de]quinoxaline-9-carboxylate (93.6 mg, 78%) was isolated as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.96 (1H, bs), 7.11-7.17 (1H, m), 6.92-6.98 (1H, s), 6.50 (1H, s), 4.86 (2H, s), 3.68-3.73 (4H, m), 2.91-3.05 (4H, m) 1.59 (9H, s) ppm.

15

Step D:

- Tert-butyl 2-oxo-2,3,7,8,10,11-hexahydro-1H,9H-azepino[4'5':4,5]pyrrolo[1,2,3-de]quinoxaline-9-carboxylate (501.4 mg, 1.5 mmol) was dissolved in DMF (5mL). The
- 20 solution was cooled to 0°C. NaH (44.5 mg, 1.76 mmol) was added. The reaction was warmed to 50 °C for 45 min. The reaction was cooled back to 0°C, and excess MeI was added. The reaction was then stirred at 0°C for 2 hrs. The reaction was quenched with a saturated aqueous solution of
- 25 NH₄Cl. The reaction was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried, and concentrated to afford 558 mg of a brown oil. This crude product was purified by column chromatography (2-5% MeOH/CH₂Cl₂) to afford tert-butyl 3-methyl-2-oxo-
- 30 2,3,7,8,10,11-hexahydro-1H,9H-azepino[4'5':4,5]pyrrolo[1,2,3-de]quinoxaline-9-carboxylate (152.9 mg, 29%) as a white amorphous solid. ¹H NMR (CDCl₃, 300 MHz) δ 7.14-7.18 (1H, m), 6.99-7.04 (1H, m), 6.63 (1H, d, J = 7.3 Hz), 4.88 (2H, s), 3.63-3.74 (4H, m), 3.46 (3H,
- 35 s), 2.89-2.99 (4H, m), 1.59 (9H, m) ppm.

Step E:

Tert-butyl 3-methyl-2-oxo-2,3,7,8,10,11-hexahydro-1H,9H-azepino[4',5':4,5]pyrrolo[1,2,3-de]quinoxaline-9-carboxylate (153.3 mg, 0.6 mmol) was dissolved in THF (20 mL). 1M BH₃·THF (2.1 mL, 2.1 mmol) was added drop-wise. The reaction was refluxed for 2 hours and then subsequently cooled to rt. 5M HCl (12 mL) was added drop-wise. After the bubbling ceased, the reaction was heated to reflux for 10 30 min, after which it was cooled to 0°C. 50% NaOH was added drop-wise until the pH=14. The reaction mixture was extracted with CHCl₃ (3 X 20 mL). The combined organic layers were washed with brine, dried, and concentrated to afford a 190 mg light-brown oil. This crude material was 15 dissolved in dioxane (4 mL) and 1M NaOH (2mL), and then Boc₂O (143 mg, 6.6 mmol) was added. The solution was stirred for 18hrs, and then it was concentrated. EtOAc (20 mL) and brine (20mL) were added to the residue and stirred for 10 min. The layers were separated, and the aqueous was 20 re-extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine, dried, and concentrated to afford 220 mg of a brown oil. This crude product was purified by column chromatography (30% acetone/hexane) to afford (120 mg, 58%) of tert-butyl (6bS,11aS)-3-methyl-25 2,3,6b,7,8,10,11,11a-octahydro-1H,9H-azepino[4',5':4,5]pyrrolo[1,2,3-de]quinoxaline-9-carboxylate as a clear oil. ¹H NMR (CDCl₃, 300 MHz) δ 6.55-6.7 (1H, m), 6.4-6.5 (1H, m), 6.37 (1H, d, J = 7.7 Hz), 3.1-3.7 (9H, m), 3.8-3.9 (4H, m), 1.7-2.1 (4H, m), 1.46 30 (9H, s) ppm.

Step F:

Tert-butyl (6bS,11aS)-3-methyl-2,3,6b,7,8,10,11,11a-octahydro-1H,9H-azepino[4',5':4,5]pyrrolo[1,2,3-de]quinoxaline-9-carboxylate (115 mg, 0.33 mmol) was 35

dissolved in 20% TFA (3 mL) in CH₂Cl₂ at rt. The reaction was stirred at rt for 2.5 hrs. Ice chips were added to the reaction, and then it was basified with 50% NaOH until pH=14. Brine (5 mL) was added and then the reaction was
5 extracted with CH₂Cl₂ (2 X 10 mL). The combined organic layers were washed with brine, dried, and concentrated to afford the title compound (84.1 mg, 103%) as a viscous oil.
1H NMR (CDCl₃, 300 MHz) δ 6.59-6.64 (1H, m), 6.48 (1H, d, J = 7.3 Hz), 6.37 (1H, d, J = 7.7 Hz), 3.4-3.7 (4H, m), 2.6-
10 3.3 (10H, m), 1.7-2.2 (4H, m) ppm. MS (ESI): 244.2 (base, M+H)

EXAMPLE 282

4-(3-methyl-2,3,6b,7,8,10,11,11a-octahydro-1H,9H-
15 azepino[4',5':4,5]pyrrolo[1,2,3-de]quinoxalin-9-yl)-1-(4-fluorophenyl)-1-butanone

3-Methyl-2,3,7,8,9,10,11,11a-octahydro-1H,6bH-
azepino[4',5':4,5]pyrrolo[1,2,3-de]quinoxaline (72 mg, 0.3
20 mmol), 4-chloro-4'-fluorobutyrophenone (119 mg, 0.6 mmol), KI (49 mg, 0.3 mmol), and DIEA (383 mg, 3 mmol) were added to dioxane (2.5 mL). The suspension was stirred at 96°C for 18 hrs. The reaction was cooled to rt and then concentrated. The residue was purified by column
25 chromatography (5-10 % MeOH/ CH₂Cl₂), to afford the title compound (37.5 mg, 31%) as an oil. The enantiomers of the title compound were separated on a Chiracel OD column using 8% EtOH-Hexane as the eluent. 1H NMR (CDCl₃, 300 MHz) δ
7.9-8.1 (2H, m), 7.1-7.2 (2H, m), 6.6-6.7 (1H, m), 6.3-6.5
30 (2H, m), 2.7-3.8 (19 H, m), 1.9-2.3 (4H, m) ppm. MS (ESI): 408.3 (base, M+H)

EXAMPLE 283

(+/-)-1,1,3-Trimethyl-2,3,6b,7,8,9,10,10a-octahydro-1H-
35 pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline

Step A:

To a solution of ethyl 2-oxo-2,3,9,10-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (from Example 211, Step A) (360 mg, 1.2 mmol) in DMF (20 mL) at rt was added NaH (172 mg, 4.8 mmol), MeI (0.25 mL, 4.0 mmol) and stirred at 25°C for 6 hours. The solution was diluted with water (30 mL) and extracted with EtOAc (2 x 30 mL). The combined extracts were dried over magnesium sulfate, concentrated, and purified by flash chromatography to afford ethyl 1,1,3-trimethyl-2-oxo-2,3,9,10-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (370 mg, 90%) as an oil.

MS [M + H]⁺ 342. ¹H NMR (CDCl₃, 300 MHz): δ 7.12 (d, 1H, J = 7.7 Hz), 7.01 (t, 1H, J = 7.7 Hz), 6.63 (d, 1H, J = 7.7 Hz), 4.69 (s, 2H), 4.23 (m, 2H), 3.86 (m, 2H), 3.43 (s, 3H), 3.01 (m, 2H), 1.81 (s, 6H), 1.24 (t, 3H, J = 7.3 Hz) ppm.

Step B:

To a solution of ethyl 1,1,3-trimethyl-2-oxo-2,3,9,10-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (240 mg, 0.7 mmol) in THF (20 mL) at 25°C was added BH₃/THF complex (0.7 mL, 0.7 mmol). The mixture was stirred at 80°C for 5 hours then cooled to rt and added 6N HCl (10 mL) with stirred for another 1 hr. About 30 mL of H₂O was added and then was extracted with EtOAc (2 x 30 mL). The combined extracts were dried over magnesium sulfate, concentrated, and purified by flash chromatography to give ethyl-1,1,3-trimethyl-2,3,9,10-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate as an oil (152 mg, 66%). MS [M + H]⁺ 327. ¹H NMR (CDCl₃, 300 MHz) δ 7.01 (t, 1H, J = 7.7 Hz), 6.97 (d,

1H, J = 7.7 Hz), 6.41 (d, 1H, J = 7.7 Hz), 4.68 (s, 2H), 4.23 (m, 2H), 3.84 (m, 2H), 3.11 (m, 2H), 2.99 (s, 3H), 1.54 (s, 6H), 1.27 (t, 3H, J = 7.3 Hz) ppm.

5 **Step C:**

To a solution of ethyl-1,1,3-trimethyl-2,3,9,10-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (69 mg, 0.21 mmol) in TFA (2 mL) at 0 °C was added NaBH₃CN (53 mg, 0.84 mmol). The mixture was stirred at rt for 4 hours, and then removed the TFA by N₂. About 10 mL of H₂O was added and then was extracted with EtOAc (2 x 10 mL). The combined extracts were dried over magnesium sulfate and concentrated to afford ethyl-1,1,3-trimethyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate as an oil which was used for the next reaction (45 mg, 65%). MS [M + H]⁺ 330.

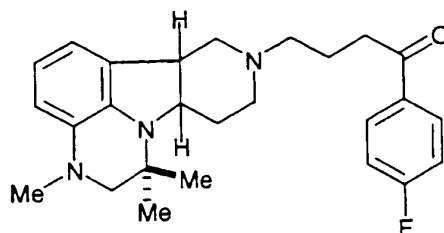
Step D:

20 To a solution of ethyl 1,1,3-trimethyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (8 mg, 0.02 mmol) in n-butanol (5 mL) at rt was added KOH (50 mg, 0.89 mmol) and stirred at 120°C for 20 hours. The solution was diluted with water (10 mL) and extracted with EtOAc (2 x 20 mL). The combined extracts were dried over magnesium sulfate and concentrated to afford the title compound (5 mg, 81%). MS [M + H]⁺ 258.

30

EXAMPLE 284

(+/-)-1-(4-Fluorophenyl)-4-(1,1,3-trimethyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-butanone

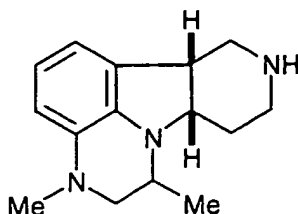


To a solution of 1,1,3-trimethyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline (from Example 283) (82 mg, 0.32 mmol) in dioxane (10 mL) at
 5 rt was added 4-chloro-1-(4-fluorophenyl)butan-1-one (83 mg, 0.42 mmol), K₂CO₃ (100 mg), KI (30 mg) and stirred at 25 °C for 24 hours. The solution was diluted with water (30 mL) and extracted with EtOAc (2 x 30 mL). The combined
 10 extracts were dried over magnesium sulfate, concentrated, and purified by flash chromatography to afford the title compound (58 mg, 43%). MS [M + H]⁺ 422. ¹H NMR (CDCl₃, 300 MHz): δ 8.01 (m, 2H), 7.15 (t, 2H, J = 7.7 Hz), 6.65 (t, 1H, J = 7.7 Hz), 6.51 (d, 1H, J = 7.0 Hz), 6.43 (d, 1H, J = 7.0 Hz), 3.63 (m, 1H), 3.25 (d, 1H, J = 11 Hz), 3.09 (m,
 15 2H), 2.89 (s, 3H), 2.63 (m, 2H), 2.25 (m, 2H), 2.17 (m, 2H), 1.31 (s, 3H), 1.12 (s, 3H) ppm. This racemate was then separated into its corresponding enantiomers by HPLC utilizing a Chiralcel AD column with 50% Ethanol/Methanol solvent system.

20

EXAMPLE 285

(+/-)-1,3-Dimethyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline



Step A:

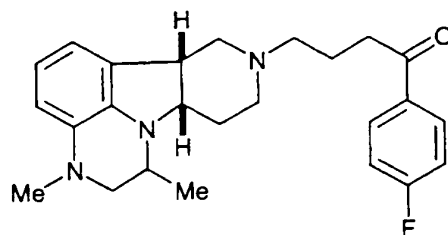
To a solution of ethyl 2-oxo-2,3,9,10-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (from Example 211, StepA) (500 mg, 1.6 mmol) in DMF (20 mL) at rt was added NaH (147 mg, 3.6 mmol), MeI (0.25 mL, 4.0 mmol) and stirred at 25°C for 3 hours. The solution was diluted with water (30 mL) and extracted with EtOAc (2 x 30 mL). The combined extracts were dried over magnesium sulfate, concentrated, and purified by flash chromatography to afford ethyl 1,3-dimethyl-2-oxo-2,3,9,10-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (350 mg, 64%) as an oil. MS [M + H]⁺ 328. ¹H NMR (CDCl₃, 300 MHz): δ 7.18 (d, 1H, J = 7.7 Hz), 7.01 (t, 1H, J = 7.7 Hz), 6.63 (d, 1H, J = 7.7 Hz), 4.90 (m, 1H), 4.51 (m, 1H), 3.20 (m, 5H), 3.49 (m, 1H), 3.42 (s, 3H), 2.91 (m, 1H), 2.80 (m, 1H), 1.61 (d, 3H, J = 7.0), 1.28 (t, 3H, J = 7.3 Hz) ppm.

20 Step B:

Following the procedure of example 283 Steps B-D to afford the title compound. MS $[M + H]^+$ 258.

EXAMPLE 286

25 4-(1,3-Dimethyl-2,3,6b,9,10,10a-hexahydro-1H-
pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-
(4-fluorophenyl)-1-butanone



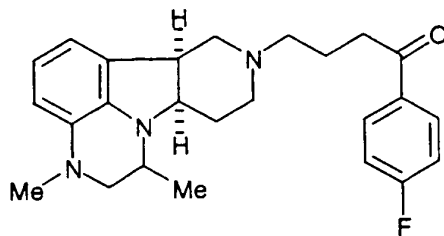
The title compound was prepared in a manner similar to that described for Example 284, utilizing 1,3-dimethyl-2,3,6b,7,8,9,10,10a-octahydro-1H-
 5 pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline from Example 285. The product was obtained as colorless oil. MS [M + H]⁺ 408. ¹H NMR (CDCl₃, 300 MHz): δ 7.89 (m, 2H), 7.15 (t, 2H, J = 8.4 Hz), 6.62 (t, 1H, J = 7.3 Hz), 6.51 (d, 1H, J = 7.4 Hz), 6.39 (d, 1H, J = 7.4 Hz), 3.63 (m, 1H), 3.52 (m,
 10 4H), 3.15 (m, 4H), 3.86 (s, 3H), 3.65 (m, 4H), 2.17 (m, 2H), 1.81 (m, 1H), 1.21 (m, 1H), 1.13 (d, 3H, J = 6.2 Hz) ppm. This racemate was then separated into its corresponding enantiomers by HPLC utilizing a Chiralcel AD column with 90% Acetonitrile/2-Propanol solvent system.

15

EXAMPLE 287

4-(1,3-dimethyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)-1-(4-fluorophenyl)-1-butanone

20



The title compound was prepared in a manner similar to that described for Example 284, utilizing 1,3-dimethyl-2,3,6b,7,8,9,10,10a-octahydro-1H-

pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline from Example 285. The product was obtained as colorless oil. MS [M + H]⁺ 408. ¹H NMR (CDCl₃, 300 MHz): δ 8.00 (m, 2H), 7.15 (m, 2H), 6.62 (t, 1H, J = 7.3 Hz), 6.51 (d, 1H, J = 7.4 Hz), 5 6.39 (d, 1H, J = 7.4 Hz), 3.63 (t, 1H, J = 5.2 Hz), 3.60 (m, 1H), 3.40 (m, 4H), 3.25 (m, 4H), 2.82 (s, 3H), 2.60 (m, 4H), 2.17 (m, 2H), 1.81 (m, 1H), 1.13 (d, 3H, J = 6.2 Hz) ppm. This racemate was then separated into its corresponding enantiomers by HPLC utilizing a Chiralcel AD 10 column with 90% Acetonitrile/2-Propanol solvent system.

EXAMPLE 288

(+/-)-5-(2,4-dichlorophenyl)-2-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline 15

Step A:

To a solution of *tert*-butyl 6-amino-1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indole-2-carboxylate (7 g, 24.3 mmol) in CH₂Cl₂ (40 mL) at rt was added saturated K₂CO₃ (30 20 mL), ethyl chloroformate (2.4 mL, 4.0 mmol) and stirred at 25°C for 0.5 hour. The solution was diluted with water (30 mL) and extracted with CH₂Cl₂ (2 x 30 mL). The combined extracts were dried over magnesium sulfate, and concentrated to afford *tert*-butyl 6- 25 [(ethoxycarbonyl)amino]-1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indole-2-carboxylate (8.7 g, 100%) as an crude oil. MS [M + H]⁺ 360.

Step B:

30 To a solution of *tert*-butyl 6-[(ethoxycarbonyl)amino]-1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indole-2-carboxylate (8.7 g, 24.3 mmol) in CH₂Cl₂ (40 mL) at rt was added TFA (20 mL) and stirred at rt for 3 hours before the solvent was removed by the nitrogen stream. The solution was 35 diluted with water (30 mL) and extracted with CH₂Cl₂ (2 x

30 mL). The combined extracts were dried over magnesium sulfate, and concentrated to afford an crude residue that was re-dissolved in CH₂Cl₂ (40 mL) followed by saturated K₂CO₃ (30 mL), ethyl chloroformate (2.4 mL, 4.0 mmol) and stirred at 25°C for 0.5 hour. The solution was diluted with water (30 mL) and extracted with CH₂Cl₂ (2 x 30 mL). The combined extracts were dried over magnesium sulfate, concentrated, and purified by flash chromatography to afford ethyl 6-[(ethoxycarbonyl)amino]-1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indole-2-carboxylate (4.5 g, 67%) as a clear oil. MS [M + H]⁺ 332. ¹H NMR (CDCl₃, 300 MHz): δ 7.00 (t, 1H, J = 7.7 Hz), 6.82 (m, 1H), 6.71 (m, 1H), 4.62 (s, 2H), 4.02-4.31 (m, 4H), 3.82 (t, 1H, J = 5.5 Hz), 2.82 (t, 1H, J = 5.5 Hz), 1.20-1.24 (m, 6H) ppm.

Step C:

To a solution of ethyl 6-[(ethoxycarbonyl)amino]-1,3,4,5-tetrahydro-2H-pyrido[4,3-b]indole-2-carboxylate (4.5 g, 13.6 mmol) in CH₂Cl₂ (40 mL) at 0°C was added TFA (20 mL) followed by NaCNBH₃ (1.8 g, 27 mmol) and stirred at rt for 3 hours before the solvent was removed by the nitrogen stream. To the resulting residue were added CH₂Cl₂ (40 mL) and 6N HCl (20 mL) and stirred for 0.5 hour. The solution was diluted with water (20 mL), 1N NaOH (30 mL) and extracted with CH₂Cl₂ (2 x 30 mL). The combined extracts were dried over magnesium sulfate, concentrated, and purified by flash chromatography to afford ethyl 6-[(ethoxycarbonyl)amino]-1,3,4,4a,5,9b-hexahydro-2H-pyrido[4,3-b]indole-2-carboxylate (3.6 g, 80%) as a clear oil. MS [M + H]⁺ 334. ¹H NMR (CDCl₃, 300 MHz): δ 6.97 (d, 1H, J = 7.3 Hz), 6.85 (d, 1H, J = 7.3 Hz), 6.72 (t, 1H, J = 7.3 Hz), 4.05 (m, 4H), 3.41 (m, 4H), 1.92 (m, 2H), 1.20-1.24 (m, 6H) ppm.

Step D:

To a solution of ethyl 6-[(ethoxycarbonyl)amino]-1,3,4,4a,5,9b-hexahydro-2H-pyrido[4,3-b]indole-2-carboxylate (2.2 g, 6.6 mmol) in DMF (20 mL) at 0°C was added NaH (660 mg, 16.5 mmol), DMAP (878 mg, 7.2 mmol),
5 acetyl chloride (0.6 mL, 7.2 mmol) and stirred at rt for 16 hours. The solution was diluted with water (30 mL), and extracted with EtOAc (2 x 30 mL). The combined extracts were dried over magnesium sulfate, concentrated, and purified by flash chromatography to afford diethyl 1-oxo-
10 6b,9,10,10a-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-3,8(2H,7H)-dicarboxylate (1.1 g, 57%) as a clear oil. MS [M + H]⁺ 374. ¹H NMR (CDCl₃, 300 MHz): δ 6.75 (t, 1H, J = 7.7 Hz), 6.59 (m, 1H), 6.45 (m, 1H), 4.05 (m, 1H), 3.60-4.00 (m, 7H), 3.40 (m, 1H), 3.00 (m, 3H),
15 1.92 (m, 2H), 0.91 (m, 1H), 0.85 (m, 6H) ppm.

Step E:

To a solution of diethyl 1-oxo-6b,9,10,10a-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-
20 3,8(2H,7H)-dicarboxylate (360 mg, 0.97 mmol) in DMF (20 mL) at 0°C was added NaH (193 mg, 4.8 mmol), MeI (0.3 mL, 4.8 mmol) and stirred at rt for 16 hours. The solution was diluted with water (20 mL), and extracted with EtOAc (2 x 20 mL). The combined extracts were dried over magnesium
25 sulfate, concentrated to afford diethyl 2-methyl-1-oxo-6b,9,10,10a-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-3,8(2H,7H)-dicarboxylate (300 mg, 80%) as a crude oil. MS [M + H]⁺ 388.

Step F:

To a solution of diethyl 2-methyl-1-oxo-6b,9,10,10a-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-3,8(2H,7H)-dicarboxylate (300 mg, 0.77 mmol)
in THF (10 mL) at rt was added BH₃THF complex (3.8 mL, 3.8
35 mmol) and refluxed for 5 hours. At rt 6N HCl (10 mL) was

added and stirred for 0.5 hour before the solution was diluted with water (20 mL), and extracted with EtOAc (2 x 20 mL). The combined extracts were dried over magnesium sulfate, concentrated, and purified by flash chromatography to afford diethyl 2-methyl-6b,9,10,10a-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-3,8(2H,7H)-dicarboxylate (200 mg, 69%) as a clear oil. MS [M + H]⁺ 374.

10 **Step G:**

To a solution of diethyl 2-methyl-6b,9,10,10a-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-3,8(2H,7H)-dicarboxylate (40 mg, 0.1 mmol) in DMF (10 mL) at 0°C was added NBS (20 mg, 0.11 mmol) and stirred at 0°C for 2 hours. The solution was diluted with water (10 mL), and extracted with EtOAc (2 x 20 mL). The combined extracts were dried over magnesium sulfate, concentrated, and purified by flash chromatography to afford diethyl 5-bromo-2-methyl-6b,9,10,10a-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-3,8(2H,7H)-dicarboxylate (40 mg, 88%) as a clear oil. MS [M + H]⁺ 454.

Step H:

25 To a solution of diethyl 5-bromo-2-methyl-6b,9,10,10a-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-3,8(2H,7H)-dicarboxylate (100 mg, 0.22 mmol) in DMF (10 mL) was added 2,4-dichlorophenyl boronic acid (63 mg, 0.33 mmol) and Na₂CO₃ (58 mg, 0.55 mmol, in 0.4 mL of H₂O). The mixture was degassed with a stream of nitrogen for 20 min and then there was added Pd(PPh₃)₄ (35 mg, 0.03 mmol) and the mixture was stirred at 100°C for 16 h. The reaction was allowed to cool to ambient temperature and was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate and brine, dried (MgSO₄),

35

filtered through Celite and concentrated in vacuo. The residue was purified by flash chromatography (elution with hexanes/ethyl acetate) to afford diethyl 5-(2,4-dichlorophenyl)-2-methyl-6b,9,10,10a-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-3,8(2H,7H)-dicarboxylate (30 mg, 29% yield) MS [M + H]⁺ 517.

Step I:

To a solution of diethyl 5-(2,4-dichlorophenyl)-2-methyl-6b,9,10,10a-tetrahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-3,8(2H,7H)-dicarboxylate (30 mg, 0.06 mmol) in 10 mL of n-BuOH was added KOH (33 mg, 0.6 mmol) and stirred at 120°C for 16 h. The reaction was allowed to cool to ambient temperature and was diluted with ethyl acetate, washed with water (10 mL). The organic layer was collected and washed with 1N HCl (10 mL) and water (10 mL). This time the aqueous layer was collected and neutralized with saturated aqueous sodium bicarbonate and extracted with EtOAc (2 x 20 mL). The combined extracts were dried over magnesium sulfate, concentrated to afford 5-(2,4-dichlorophenyl)-2-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline (10 mg, 45%) as a solid. MS [M + H]⁺ 374.

UTILITY

The compounds of the present invention have therapeutic utility for illnesses or disorders involving the neurotransmitter serotonin (5-hydroxy tryptamine or 5-HT) and either agonism or antagonism of 5-HT₂ receptors, as demonstrated by the assays described below. Therapeutic utility for these illnesses or disorders could involve numerous biological processes affected by serotonin including, but not limited to, appetite, mood, sleep, sexual activity, and arterial constriction. These biological processes may also be important to numerous

central nervous system (CNS) disorders including those related to the affective disorders of depression, anxiety, psychosis, and schizophrenia, as well as, disorders of food intake such as anorexia, bulimia, and obesity. The

5 compounds of the present invention potentially have therapeutic utility in other conditions in which serotonin has been implicated, such as migraine, attention deficit disorder or attention deficit hyperactivity disorder, addictive behavior, and obsessive-compulsive disorder, as

10 well as, conditions associated with cephalic pain, social phobias, and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility. Lastly, compounds of the present invention potentially have therapeutic utility in neurodegenerative diseases and traumatic

15 conditions represented by the examples of Alzheimer's disease and brain/spinal cord trauma.

The pharmacological analysis of each compound for either antagonism or agonism of at 5-HT_{2A} and 5-HT_{2C} receptors consisted of in vitro and in vivo studies. In

20 vitro analyses included K_i determinations at 5-HT_{2A} and 5-HT_{2C} receptors and an assessment of functional (i.e., agonism or antagonism) activity at each receptor class by IP₃ hydrolysis assays. Additional receptor assays were conducted to evaluate receptor specificity of 5-HT_{2A} and 5-

25 HT_{2C} receptors over monoamine and nuisance receptors (e.g. histamine, dopamine, and muscarinic). A compound is considered active as a 5-HT_{2A} antagonist or a 5-HT_{2C} agonist if it has an IC₅₀ value or a K_i value of less than about 1 micromolar; preferably less than about 0.1

30 micromolar; more preferably less than about 0.01 micromolar. Compounds of the invention have been shown to have an IC₅₀ value of less than about 1 micromolar for 5-HT_{2A} antagonism or a 5-HT_{2C} agonism.

In vivo assays assessed compound activity in a variety

35 of behavioral paradigms including quipazine head twitch,

acute and chronic feeding models, anxiety and depression models (learned-helplessness, elevated plus maze, Geller-Siefter, conditioned taste aversion, taste reactivity, satiety sequence). In aggregate, these models reflect
5 activity as a 5-HT_{2A} antagonist (quipazine head twitch, depression models) or 5-HT_{2C} agonist (feeding models, anxiety models, depression models) and provide some indication as to bioavailability, metabolism and pharmacokinetics.

10 Radioligand binding experiments were conducted on recombinant human 5-HT_{2A} and 5-HT_{2C} receptors expressed in HEK293E cells. The affinities of compounds of the present invention to bind at these receptors is determined by their capacity to compete for [¹²⁵I]-1-(2,5-dimethoxy-4-
15 iodophenyl)-2-amino-propane (DOI) binding at the 5-HT_{2A} or 5-HT_{2C}. General references for binding assays include 1) Lucaites VL, Nelson DL, Wainscott DB, Baez M (1996) Receptor subtype and density determine the coupling repertoire of the 5-HT₂ receptor subfamily. Life Sci.,
20 59(13):1081-95. J Med Chem 1988 Jan;31(1):5-7; 2) Glennon RA, Seggel MR, Soine WH, Herrick-Davis K, Lyon RA, Titeler M (1988) [¹²⁵I]-1-(2,5-dimethoxy-4-iodophenyl)-2-amino-propane: an iodinated radioligand that specifically labels the agonist high-affinity state of 5-HT₂ serotonin
25 receptors. J Med. Chem. 31(1):5-7 and 3) Leonhardt S, Gorospe E, Hoffman BJ, Teitler M (1992) Molecular pharmacological differences in the interaction of serotonin with 5-hydroxytryptamine_{1C} and 5-hydroxytryptamine₂ receptors. Mol Pharmacol., 42(2):328-35.

30 The functional properties of compounds (efficacy and potency) were determined in whole cells expressing 5-HT_{2A} or 5-HT_{2C} receptors by assessing their ability to stimulate or inhibit receptor-mediated phosphoinositol hydrolysis. The procedures used are described below.

35

In Vitro Binding Assays

Stable expression of 5-HT2A and 5-HT2C receptors in HEK293E cells.

Stable cell lines were generated by transfecting
5 293EBNA cells with plasmids containing human 5-HT2A , 5-HT2B, or 5-HT2C (VNV edited isoform) cDNA using calcium phosphate. These plasmids also contained the
cytomegalovirus (CMV) immediate early promoter to drive
receptor expression and EBV oriP for their maintenance as
10 an extrachromosomal element, and the hph gene from E. Coli to yield hygromycin B resistance (Horlick et al., 1997). Transfected cells were maintained in Dulbecco's Modified Eagle medium (DMEM) containing dialyzed 10% fetal bovine serum at 37°C in a humid environment (5% CO₂) for 10 days.
15 The 5-HT2A cells were adapted to spinner culture for bulk processing whereas it was necessary to maintain the other lines as adherent cultures. On the day of harvest, cells were washed in phosphate-buffered saline (PBS), counted, and stored at -80 °C.

20

Membrane Preparation

On the day of assay, pellets of whole cells
(containing approximately 1 X 10⁸ cells) expressing the 5-HT2A or 5-HT2C receptor were thawed on ice and homogenized
25 in 50 mM Tris HCl (pH 7.7) containing 1.0 mM EDTA using a Brinkman Polytron (PT-10, setting 6 for 10 sec). The homogenate was centrifuged at 48,000 x g for 10 min and the resulting pellet washed twice by repeated homogenization and centrifugation steps. The final pellet was resuspended
30 in tissue buffer and protein determinations were made by the bichichoninic acid (BCA) assay (Pierce Co., IL) using bovine serum albumin as the standard.

Radioligand binding assays for the 5-HT2A ,and 5-HT2C
35 receptors.

Radioligand binding studies were conducted to determine the binding affinities (K_i values) of compounds for the human recombinant 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors (Fitzgerald et al., 1999). Assays were conducted in disposable polypropylene 96-well plates (Costar Corp., Cambridge, MA) and were initiated by the addition of 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} membrane homogenate in tissue buffer (10-30 (g/well) to assay buffer (50 mM Tris HCl, 0.5 mM EDTA, 10 mM pargyline, 10 mM MgSO₄, 0.05 % ascorbic acid, pH 7.5) containing [¹²⁵I]DOI for the 5-HT_{2A} and 5-HT_{2C} receptors (0.3-0.5 nM, final) or [³H]LSD (2-2.5 nM, final) for the 5-HT_{2B} receptor, with or without competing drug (i.e, newly synthesized chemical entity). For a typical competition experiment, a fixed concentration of radioligand was competed with duplicate concentrations of ligand (12 concentrations ranging from 10 picomolar to 10 micromolar). The reaction mixtures were incubated to equilibrium for 45 min at 37°C and terminated by rapid filtration (cell harvester; Inotech Biosystems Inc., Lansing, MI) over GFF glass-fiber filters that had been pre-soaked in 0.3% polyethyleneimine. Filters were washed in ice-cold 50 mM Tris HCl buffer (pH 7.5) and then counted in a gamma counter for the 5-HT_{2A} and 5-HT_{2C} assays, or by liquid scintillation spectroscopy for the 5-HT_{2B} assay.

25

Phosphoinositide hydrolysis studies.

The ability of newly synthesized compounds to stimulate phosphoinositide (PI) hydrolysis was monitored in whole cells using a variant (Egan et al., 1998) of a protocol described previously (Berridge et al., 1982). HEK293E cells expressing the human 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} receptor were lifted with 0.5 mM EDTA and plated at a density of 100,000/well onto poly-D-lysine-coated 24-well plates (Biocoat; Becton Dickinson, Bedford, MA) in Dulbecco's modified Eagle's serum (DMEM; Gibco BRL)

35

containing high glucose, 2mM glutamine, 10% dialyzed fetal calf serum, 250 (g/ml hygromycin B, and 250 (g/ml G418. Following a 24-48 hr period, the growth media was removed and replaced with DMEM without fetal calf serum and

5 inositol (Gibco BRL). The cells were then incubated with DMEM (without serum and inositol) containing a final concentration of 0.5 uCi/well myo-[³H]inositol for 16-18 hr. Following this incubation, the cells were washed with DMEM (without serum or inositol) containing 10 mM LiCl and

10 10 (M pargyline and then incubated for 30 min with the same media but now containing one of several test compounds. Reactions were terminated by aspirating the media and lysing the cells by freeze-thaw. [³H]phosphoinositides were extracted with chloroform/methanol (1:2 v/v),

15 separated by anion exchange chromatography (Bio-Rad AGI-X8 resin), and counted by liquid scintillation spectroscopy as described previously (Egan et al., 1998).

Data analyses

20 The equilibrium apparent dissociation constants (K_i's) from the competition experiments were calculated using an iterative nonlinear regression curve-fitting program (GraphPad Prism; San Diego, CA). For the PI hydrolysis experiments, EC₅₀'s were calculated using a one-site

25 'pseudo' Hill model: $y = ((R_{max} - R_{min}) / (1 + R / EC_{50})^{nH}) + R_{min}$ where R = response (DeltaGraph, Monterey, CA). E_{max} (maximal response) was derived from the fitted curve maxima (net IP stimulation) for each compound. Intrinsic activity (IA) was determined by expressing the E_{max} of a compound as a

30 percentage of the E_{max} of 5-HT (IA=1.0).

In Vivo Experiments for Serotonergic Ligands.

Preclinical Efficacy, Potency, and Side Effect Liability.

35 a) Anti-Serotonin Efficacy.

Antagonism of Quipazine-Induced Head Twitch in Rat. Quipazine, an agonist at 5-HT receptors, produces a characteristic head twitch response in rats. 5-HT receptor antagonists effectively antagonize this 5-HT agonist-induced behavioral effect (Lucki et al., 1984). Accordingly, the quipazine-induced head twitch model in rat can function as an in vivo behavioral correlate to 5-HT receptor binding. Compounds are administered 30 minutes before behavioral testing (and 25 minutes before quipazine), and a dose-related antagonism of the quipazine response is determined.

b) Antipsychotic Efficacy.

Inhibition of the Conditioned Avoidance Response (CAR) in Rat. Rats are trained to consistently avoid (by climbing onto a pole suspended from the ceiling of the test chamber) an electric foot shock (0.75 mA) delivered to the grid floor of the testing chamber. All antipsychotic drugs effectively inhibit this conditioned avoidance response (Arnt, 1982). The ability of a compound to inhibit this response is used to determine the antipsychotic efficacy of potential drug candidates.

c) Extrapyramidal Side Effect Liability.

Induction of Catalepsy in Rat. Typical antipsychotic drugs produce extrapyramidal side effects (EPS) at clinically effective doses. The most widely accepted preclinical indicator of EPS liability in humans is a drug-induced catalepsy syndrome in rat (Costall and Naylor, 1975), a condition whereby the animal will remain immobile in an externally imposed posture (analogous to a catatonic stupor in humans). Rats are tested for induction of catalepsy in a dose-response test after oral administration of compounds.

d) CNS penetration; In vivo brain receptor occupancy.

In Vivo Binding. To determine the level of in vivo receptor occupancy, an in vivo receptor binding protocol is used. This procedure uses an appropriate radioligand to label the receptor of interest. For example, to measure
5 both Dopamine D2 and 5-HT2A receptors in vivo, one can use ^3H -N-methyl spiperone (^3H -NMSP), (Frost, et. al. 1987) The procedure uses rats (or mice) fasted overnight. To measure the effects of compounds on the receptors of interest, compounds are dosed, usually p.o. for example in
10 2 microliters/gram body weight in 0.25% Methocel suspension. The radiolabeled compound (in this example, ^3H -NMSP) is administered by i.v. tail vein injection (10 microcuries label/200 gram rat). Time course experiments are used to determine the optimal time of binding for both
15 the radiolabeled and unlabeled compound. These optimal time frames are used for all subsequent dose-response experiments. After the appropriate time frame of compound/radioligand exposure, the animals are sacrificed and the relevant brain regions dissected (frontal cortex
20 for 5-HT2A and striatum for D2 receptors) and examined for their content of radioactivity. The level of non-specific binding is determined by examining a brain region known not to contain the receptor of interest (in this case the cerebellum) or by administering an excess of compound known
25 pharmacologically to interact with the receptor.

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30

Dosage and Formulation

The serotonin agonist and serotonin antagonist compounds of this invention can be administered as treatment for the control or prevention of central nervous system disorders including obesity, anxiety, depression, 35 psychosis, schizophrenia, sleep and sexual disorders, migraine and other conditions associated with cephalic

pain, social phobias, and gastrointestinal disorders such as dysfunction of the gastrointestinal tract motility by any means that produces contact of the active agent with the agent's site of action, i.e., 5-HT₂ receptors, in the
5 body of a mammal. It can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as an individual therapeutic agent or in a combination of therapeutic agents. It can be administered alone, but preferably is administered with a
10 pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules
15 (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular
20 form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts.

The dosage administered will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and
25 route of administration; the age, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; and the effect desired. By way of general guidance, a daily dosage of active ingredient can be expected to be about
30 0.001 to about 1000 milligrams per kilogram of body weight, with the preferred dose being about 0.01 to about 100 mg/kg; with the more preferred dose being about 0.1 to about 30 mg/kg. Advantageously, compounds of the present invention may be administered in a single daily dose, or
35 the total daily dosage may be administered in divided doses of two, three, or four times daily.

Dosage forms of compositions suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be
5 present in an amount of about 0.5-95% by weight based on the total weight of the composition. The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets and powders, or in liquid dosage forms, such as elixirs, syrups and suspensions. It can also be
10 administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed
15 tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the
20 atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract. Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous
25 dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing
30 agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts, and sodium EDTA. In addition, parenteral solutions
35 can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben and chlorobutanol. Suitable

pharmaceutical carriers are described in Remington's *Pharmaceutical Sciences*, supra, a standard reference text in this field.

Useful pharmaceutical dosage-forms for administration
5 of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules can be prepared by
10 filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose, and 6 mg magnesium stearic.

Soft Gelatin Capsules

15 A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil can be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules should then
20 be washed and dried.

Tablets

A large number of tablets can be prepared by conventional procedures so that the dosage unit is 100 mg
25 of active ingredient, 0.2 mg of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch and 98.8 mg of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

30

Suspension

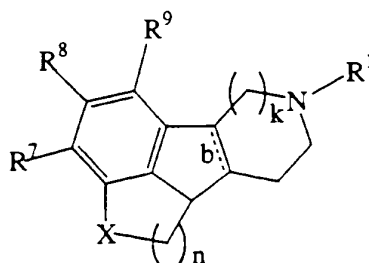
An aqueous suspension can be prepared for oral administration so that each 5 ml contain 25 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl
35 cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mg of vanillin.

Injectable

A parenteral composition suitable for administration by injection can be prepared by stirring 1.5% by weight of
5 active ingredient in 10% by volume propylene glycol and water. The solution is sterilized by commonly used techniques.

The Tables below provide representative Examples, the
10 synthesis of which are described above, of the the compounds of Formula (I) of the present invention.

Table 1

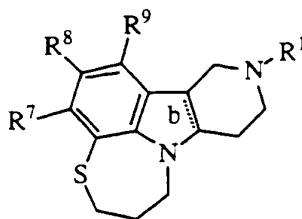


Ex#	X	n	k	R7	R8	R9	b	R1
196	NHCO	1	1	H	H	H	dbl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
210	NMe	2	1	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-pyridyl)
211	NH	2	1	H	H	H	sgl	H
212	NH	2	1	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
217	NMe	2	1	H	H	H	sgl	
218	NMe	2	1	H	H	H	sgl	
255	NMe	2	1	H	H	H	sgl	H
256	NEt	2	1	H	H	H	sgl	H
257	NPr	2	1	H	H	H	sgl	H
258	N(i-Pr)	2	1	H	H	H	sgl	H
259	N(n-Bu)	2	1	H	H	H	sgl	H
260	N(CH ₂ Ph)	2	1	H	H	H	sgl	H
261	NMe	2	1	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
262	NEt	2	1	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
263	N(i-Pr)	2	1	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
264	N(CH ₂ Ph)	2	1	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
269	NMe	2	1	H	H	H	sgl	-(CH ₂) ₃ O (4-F-phenyl)
274	NMe	2	1	H	2,4-diCl-phenyl	H	sgl	H
275	NH	2	1	H	2,4-diCl-phenyl	H	sgl	H
276	NMe	2	1	H	Br	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
277	NMe	2	1	H	MeO	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
278	NMe	2	1	H	2,4-diCl-phenyl	H	sgl	H

Table 1 cont.

Ex#	X	n	k	R7	R8	R9	b	R1
279	NH	3	1	H	4-MeO-2-Me-phenyl	H	sg1	H
280	NHCO	2	1	H	2,4-diCl-phenyl	H	sg1	H
281	NMe	2	2	H	H	H	sg1	H
282	NMe	2	2	H	H	H	sg1	-(CH ₂) ₃ C(=O)(4-F-phenyl)
283	NHCH(Me)	1	1	H	2,4-diCl-phenyl	H	sg1	H

Table 2



Ex#	R7	R8	R9	b	R1
4	H	H	F	dbl	-CO ₂ Et
5	H	H	F	dbl	H
6	H	H	Me	dbl	H
7	H	H	Me	dbl	-CO ₂ -tBu
8	H	H	Me	sgl	H
9	H	H	H	sgl	H
10	H	H	NO ₂	dbl	H
11	H	H	NO ₂	sgl	H
12	Cl	H	H	dbl	H
13	Cl	H	H	sgl	H
14	Me	H	H	dbl	H
15	Me	H	H	sgl	H
18	H	H	Br	dbl	H
19	H	H	Br	sgl	H
25	H	H	H	sgl	-C(=O) (3,4-diMeO-phenyl)
26	H	H	H	sgl	-C(=O) (2,5-diMeO-phenyl)
27	H	H	H	sgl	-C(=O) (3,5-diMeO-phenyl)
28	H	H	H	sgl	2,6-diMeO-benzyl
29	H	H	H	sgl	2,4-diMeO-benzyl
30	H	H	H	sgl	2,4,6-triMeO-benzyl
31	H	H	H	sgl	2,3-diMeO-benzyl
32	H	H	H	sgl	2,4,5-triMeO-benzyl
33	H	H	H	sgl	cyclohexylmethyl
34	H	H	H	sgl	2,3,4-triMeO-benzyl
35	H	H	H	sgl	3,4-diMeO-benzyl
36	H	H	H	sgl	3,4,5-triMeO-benzyl
39	H	H	H	sgl	-CO ₂ Et
40	H	-C(=O)CH ₃	H	sgl	-CO ₂ Et
41	H	-NHC(=O)CH ₃	H	sgl	-CO ₂ Et

Table 2 cont.

Ex#	R7	R8	R9	b	R1
42	H	H	H	sgl	-CH ₂ CH ₂ (4-F-phenyl)
43	H	H	H	sgl	Et
44	H	H	H	sgl	Pr
45	H	H	H	sgl	butyl
46	H	H	H	sgl	pentyl
47	H	H	H	sgl	hexyl
48	H	H	H	sgl	2-propyl
49	H	H	H	sgl	2-butyl
50	H	H	H	sgl	2-pentyl
51	H	H	H	sgl	2-hexyl
52	H	H	H	sgl	2-Me-propyl
53	H	H	H	sgl	2-Me-butyl
54	H	H	H	sgl	2-Me-pentyl
55	H	H	H	sgl	2-Et-butyl
56	H	H	H	sgl	3-Me-pentyl
57	H	H	H	sgl	3-Me-butyl
58	H	H	H	sgl	4-Me-pentyl
59	H	H	H	sgl	cyclopropylmethyl
60	H	H	H	sgl	cyclobutylmethyl
61	H	H	H	sgl	cyclohexylmethyl
62	H	H	H	sgl	2-propenyl
63	H	H	H	sgl	2-Me-2-propenyl
64	H	H	H	sgl	trans-2-butenyl
65	H	H	H	sgl	3-Me-butenyl
66	H	H	H	sgl	3-butenyl
67	H	H	H	sgl	trans-2-pentenyl
68	H	H	H	sgl	cis-2-pentenyl
69	H	H	H	sgl	4-pentenyl
70	H	H	H	sgl	4-Me-3-pentenyl
71	H	H	H	sgl	3,3-diCl-2-propenyl
72	H	H	H	sgl	benzyl
73	H	H	H	sgl	2-Me-benzyl
74	H	H	H	sgl	3-Me-benzyl
75	H	H	H	sgl	4-Me-benzyl
76	H	H	H	sgl	2,5-diMe-benzyl
77	H	H	H	sgl	2,4-diMe-benzyl
78	H	H	H	sgl	3,5-diMe-benzyl
79	H	H	H	sgl	2,4,6-triMe-benzyl

Table 2 cont.

Ex#	R7	R8	R9	b	R1
80	H	H	H	sgl	3-MeO-benzyl
81	H	H	H	sgl	3,5-diMeO-benzyl
82	H	H	H	sgl	pentafluorobenzyl
83	H	H	H	sgl	2-phenylethyl
84	H	H	H	sgl	1-phenyl-2-propyl
85	H	H	H	sgl	trans-3-phenyl-2-propenyl
86	H	H	H	sgl	4-phenylbutyl
87	H	H	H	sgl	4-phenylbenzyl
88	H	H	H	sgl	2-phenylbenzyl

Table 2 cont.

5

Ex#	R7	R8	R9	b	R1
169	H	Me	H	sgl	H
170	H	CN	H	sgl	H
171	H	Et	H	sgl	H
175	H	H	H	dbl	Me
176	H	H	H	sgl	Me
177	H	H	H	sgl	H
178	Cl	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
179	Me	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
180	H	H	H	sgl	-(CH ₂) ₃ S (3-F-phenyl)
181	H	H	H	sgl	-(CH ₂) ₃ CH(OH) (4-F-phenyl)
186	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
187	H	MeO	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
192	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-Br-phenyl)
193	H	H	H	sgl	-(CH ₂) ₃ SO ₂ (3-F-phenyl)
194	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-(3,4-diCl-phenyl)phenyl)
197	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-Me-phenyl)
198	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
199	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-MeO-phenyl)
200	H	H	H	sgl	-(CH ₂) ₂ C(=O) (4-F-phenyl)

Table 2 cont.

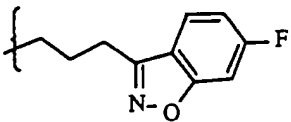
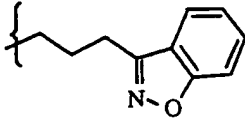
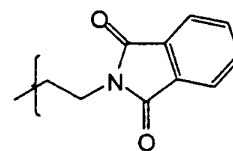
Ex#	R7	R8	R9	b	R1
201	H	H	H	sgl	$-(CH_2)_3SO_2(4-F-phenyl)$
202	H	H	H	sgl	$-(CH_2)_3S(=O)(4-F-phenyl)$
203	H	H	H	sgl	$-(CH_2)_3O(4-F-phenyl)$
204	H	H	H	sgl	$-(CH_2)_3O(phenyl)$
205	H	H	H	sgl	$-(CH_2)_3S(4-F-phenyl)$
206	H	H	H	sgl	$-(CH_2)_3NH(4-F-phenyl)$
207	H	H	H	sgl	$-(CH_2)_3N(CH_3)(4-F-phenyl)$
208	H	H	H	sgl	$-(CH_2)_3C(=O)(4-pyridyl)$
209	H	H	H	sgl	$-(CH_2)_3C(=O)(3-pyridyl)$
214	H	H	H	sgl	
215	H	H	H	sgl	
219	H	H	H	sgl	$-(CH_2)_3CO_2Et$
220	H	H	H	sgl	$-(CH_2)_4CO_2Et$
221	H	H	H	sgl	$-(CH_2)_3C(=O)N(CH_3)(OCH_3)$
222	H	H	H	sgl	$-(CH_2)_4C(=O)N(CH_3)(OCH_3)$
223	H	H	H	sgl	$-(CH_2)_3C(=O)(3-Me-4-F-phenyl)$
224	H	H	H	sgl	$-(CH_2)_3C(=O)(phenyl)$
225	H	H	H	sgl	$-(CH_2)_3C(=O)(4-Cl-phenyl)$
226	H	H	H	sgl	$-(CH_2)_3C(=O)(3-Me-phenyl)$
227	H	H	H	sgl	$-(CH_2)_3C(=O)(4-tBu-phenyl)$
228	H	H	H	sgl	$-(CH_2)_3C(=O)(3,4-diF-phenyl)$
229	H	H	H	sgl	$-(CH_2)_3C(=O)(2-MeO-5-F-phenyl)$
230	H	H	H	sgl	$-(CH_2)_4C(=O)(phenyl)$
231	H	H	H	sgl	$-(CH_2)_3C(=O)(4-F-1-naphthyl)$
232	H	H	H	sgl	$-(CH_2)_3C(=O)(benzyl)$
233	H	H	H	sgl	$-(CH_2)_2C(=O)NH(4-F-phenyl)$
234	H	H	H	sgl	$-(CH_2)_3C(=O)NH(4-F-phenyl)$

Table 2 cont.

Ex#	R7	R8	R9	b	R1
235	H	H	H	sgl	$-(CH_2)_3CH(OH)(4-F-phenyl)$
236	H	H	H	sgl	$-(CH_2)_3CH(OH)(4-pyridyl)$
237	H	H	H	sgl	$-(CH_2)_3CH(OH)(2,3-diMeO-phenyl)$
238	H	H	H	sgl	$-(CH_2)_3C(=O)(2,3-diMeO-phenyl)$
239	H	H	H	sgl	$-(CH_2)_4(cyclohexyl)$
240	H	H	H	sgl	$-(CH_2)_3CH(phenyl)_2$
241	H	H	H	sgl	$-CH_2CH_2CH=C(phenyl)_2$
242	H	H	H	sgl	$-(CH_2)_3CH(4-F-phenyl)_2$
243	H	H	H	sgl	$-CH_2CH_2CH=C(4-F-phenyl)_2$
244	H	H	H	sgl	$-(CH_2)_2NHC(=O)(phenyl)$
245	H	H	H	sgl	$-(CH_2)_2NHC(=O)(2-F-phenyl)$
246	H	H	H	sgl	$-(CH_2)_2NHC(=O)(4-F-phenyl)$
247	H	H	H	sgl	$-(CH_2)_3(3-indolyl)$
248	H	H	H	sgl	$-(CH_2)_3(1-Me-3-indolyl)$
249	H	H	H	sgl	$-CH_2CH_2(3-indolyl)$
250	H	H	H	sgl	$-(CH_2)_3(1-indolyl)$
251	H	H	H	sgl	$-(CH_2)_3(1-indolyl)$
252	H	H	H	sgl	$-(CH_2)_3(1-benzimidazolyl)$

253 H H H sgl



254 H H H sgl

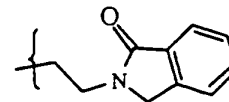


Table 2 cont.

Ex#	R7	R8	R9	b	R1
268		H	F	H	sgl - (CH ₂) ₃ C(=O) (4-F-phenyl)
271		H	H	H	sgl H
273		H	F	H	sgl H
S274		Br	H	H	sgl H
S275	2,6-diF-phenyl		H	H	sgl H
S276	2-Me-4-MeO-phenyl		H	H	sgl H
S277	4-CF ₃ -phenyl		H	H	sgl H
S278	2,3-diCl-phenyl		H	H	sgl H
S279	2,4-diCl-phenyl		H	H	sgl H
S280	2-Cl-4-CF ₃ -phenyl		H	H	sgl H
S281		CN	H	H	sgl H
S282		CN	Br	H	sgl H
S283		benzyl	H	H	sgl H
284		CHO	H	H	sgl H
285		CO ₂ H	H	H	sgl H
286		H	H	H	sgl - (CH ₂) ₂ NHC(=O) (2,4-diF-phenyl)
287		H	H	H	sgl - (CH ₂) ₂ NMeC(=O)-phenyl
288		H	H	H	sgl - (CH ₂) ₂ NMeC(=O) (2-F-phenyl)
289		H	H	H	sgl - (CH ₂) ₂ NMeC(=O) (2,4-diF-phenyl)
290		H	H	H	sgl - (CH ₂) ₂ NMeC(=O) (4-F-phenyl)
291		H	H	H	sgl - (CH ₂) ₃ (1H-1,2,3-benzotriazol-1-yl)
292		H	H	H	sgl - (CH ₂) ₃ (1H-1,2,3-benzotriazol-2-yl)

Table 2 cont.

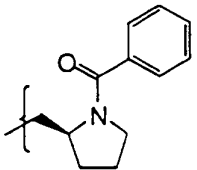
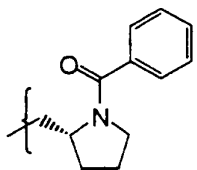
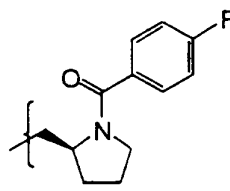
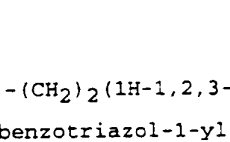
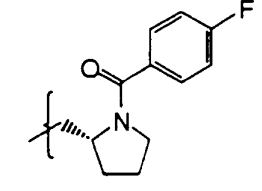
Ex#	R7	R8	R9	b	R1
293		H	H	H	
294		H	H	H	
295		H	H	H	
296		H	H	H	
297		H	H	H	

Table 2 cont.

Ex#	R7	R8	R9	b	R1
298		H	H	H	sgl $-(CH_2)_2(1H-1,2,3-$ benzotriazol-2-yl)
299		H	H	H	sgl $-(CH_2)_3(3,4-dihydro-$ 1(2H)-quinolinyl)
300		H	H	H	sgl $-CH_2CH_2CH=CMe(4-F-$ phenyl)
301		H	H	H	sgl $-(CH_2)_2(2,3-dihydro-1H-$ inden-2-yl)
302		H	H	H	sgl $-(CH_2)_3C(=O)(2-NH_2-$ phenyl)
303		H	H	H	sgl $-(CH_2)_3C(=O)(2-NH_2-$ phenyl)
304		H	H	H	sgl $-(CH_2)_3C(=O)(2-NH_2-5-F-$ phenyl)
305		H	H	H	sgl $-(CH_2)_3C(=O)(2-NH_2-3-F-$ phenyl)
306		H	H	H	sgl $-(CH_2)_3C(=O)(2-NH_2-4-$ Cl-phenyl)
307		H	H	H	sgl $-(CH_2)_3C(=O)(2-NH_2-4-$ OH-phenyl)
308		H	H	H	sgl $-(CH_2)_3C(=O)(2-NH_2-4-$ Br-phenyl)
309		H	H	H	sgl $-(CH_2)_3(1H-indazol-3-$ yl)

Table 2 cont.

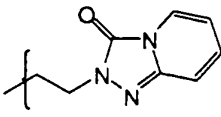
Ex#	R7	R8	R9	b	R1
310		H	H	H	sgl $-(CH_2)_3(5-F-1H-indazol-3-yl)$
311		H	H	H	sgl $-(CH_2)_3(7-F-1H-indazol-3-yl)$
312		H	H	H	sgl $-(CH_2)_3(6-Cl-1H-indazol-3-yl)$
313		H	H	H	sgl $-(CH_2)_3(6-Br-1H-indazol-3-yl)$
314		H	H	H	sgl $-(CH_2)_3C(=O)(2-NHMe-phenyl)$
315		H	H	H	sgl $-(CH_2)_3(1-benzothien-3-yl)$
355		H	H	H	sgl 
356		H	H	H	sgl $-(CH_2)_3(6-F-1H-indol-1-yl)$
357		H	H	H	sgl $-(CH_2)_3(5-F-1H-indol-1-yl)$
358		H	H	H	sgl $-(CH_2)_3(6-F-2,3-dihydro-1H-indol-1-yl)$
359		H	H	H	sgl $-(CH_2)_3(5-F-2,3-dihydro-1H-indol-1-yl)$

Table 2 cont.

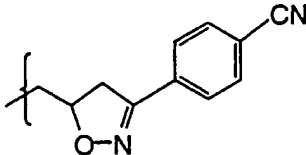
Ex#	R7	R8	R9	b	R1
360		H	H	H	sgl $-(CH_2)_3(6-F-1H-indol-3-yl)$
361		H	H	H	sgl $-(CH_2)_3(6-F-1H-indol-3-yl)$
362		H	H	H	sgl $-(CH_2)_3(5-F-1H-indol-3-yl)$
363		H	H	H	sgl $-(CH_2)_3(5-F-1H-indol-3-yl)$
364		H	H	H	sgl $-(CH_2)_3(9H-purin-9-yl)$
365		H	H	H	sgl $-(CH_2)_3(7H-purin-7-yl)$
366		H	H	H	sgl 
367		H	H	H	sgl $-(CH_2)_3(6-F-1H-indazol-3-yl)$
368		H	H	H	sgl $-(CH_2)_3(6-F-1H-indazol-3-yl)$
369		H	H	H	sgl $-(CH_2)_3(6-F-1H-indazol-3-yl)$
370		H	H	H	sgl $-(CH_2)_3C(=O)(2-NH_2-4-F-phenyl)$

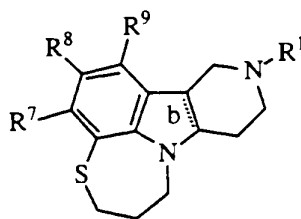
Table 2 cont.

Ex#	R7	R8	R9	b	R1
371		H	H	H	sg1 $-(CH_2)_3C(=O)(2-NH_2-4-F-phenyl)$
372		H	H	H	sg1 $-(CH_2)_3C(=O)(2-NHSO_2Me-4-F-phenyl)$
373		H	H	H	sg1 $-(CH_2)_3C(=O)(2-NHC(=O)Me-4-F-phenyl)$
374		H	H	H	sg1 $-(CH_2)_3C(=O)(2-NHC(=O)Me-4-F-phenyl)$
375		H	H	H	sg1 $-(CH_2)_3C(=O)(2-NHCO_2Et-4-F-phenyl)$
376		H	H	H	sg1 $-(CH_2)_3C(=O)(2-NHC(=O)NHEt-4-F-phenyl)$
377		H	H	H	sg1 $-(CH_2)_3C(=O)(2-NHCHO-4-F-phenyl)$
378		H	H	H	sg1 $-(CH_2)_3C(=O)(2-OH-4-F-phenyl)$
379		H	H	H	sg1 $-(CH_2)_3C(=O)(2-MeS-4-F-phenyl)$
442		H	H	H	sg1 $-(CH_2)_3C(=O)(2-NHSO_2Me-4-F-phenyl)$
485		H	H	H	sg1 $-(CH_2)_2C(Me)CO_2Me$
486		H	H	H	sg1 $-(CH_2)_2C(Me)C(OH)(4-F-phenyl)_2$

Table 2 cont.

Ex#	R7	R8	R9	b	R1
487		H	H	H	sgl $-(CH_2)_2C(Me)C(OH)(4-Cl-phenyl)_2$
489		H	H	H	sgl $-(CH_2)_2C(Me)C(=O)(4-F-phenyl)$
490		H	H	H	sgl $-(CH_2)_2C(Me)C(=O)(2-MeO-4-F-phenyl)$
491		H	H	H	sgl $-(CH_2)_2C(Me)C(=O)(3-Me-4-F-phenyl)$
492		H	H	H	sgl $-(CH_2)_2C(Me)C(=O)(2-Me-phenyl)$
493		H	H	H	sgl $-(CH_2)_2C(Me)C(=O)phenyl$
591		Cl	H	H	sgl $-(CH_2)_3C(=O)(2-NH_2-4-F-phenyl)$

Table 2A



Ex#	R7	R8	R9	b	R1
115	H	H	Br	dbl	-CO ₂ -tBu
116	H	H	2,3-diCl-phenyl	dbl	-CO ₂ -tBu
117	H	H	3,4-diCl-phenyl	dbl	-CO ₂ -tBu
118	H	H	2-Cl-4-CF ₃ -phenyl	dbl	-CO ₂ -tBu
119	H	H	2,3-diCl-phenyl	dbl	H
120	H	H	3,4-diCl-phenyl	dbl	H
121	H	H	2-Cl-4-CF ₃ -phenyl	dbl	H
122	H	H	2,3-diCl-phenyl	sgl	H
123	H	H	3,4-diCl-phenyl	sgl	H
124	H	H	2-Cl-4-CF ₃ -phenyl	sgl	H
125	H	H	Br	sgl	-CO ₂ -tBu
126	H	H	2,6-diF-phenyl	sgl	-CO ₂ -tBu
127	H	H	2,6-diF-phenyl	sgl	H
128	H	2,4-diCl-phenyl	H	sgl	H
129	H	phenyl	H	sgl	H
130	H	4-F-phenyl	H	sgl	H
131	H	4-Cl-phenyl	H	sgl	H
132	H	2-Cl-phenyl	H	sgl	H
133	H	2-MeO-phenyl	H	sgl	H
134	H	2-Cl-4-CF ₃ -phenyl	H	sgl	H
135	H	2,4-diMe-phenyl	H	sgl	H
136	H	2-Cl-4-MeO-phenyl	H	sgl	H
137	H	4-iPr-phenyl	H	sgl	H
138	H	4-Bu-phenyl	H	sgl	H
139	H	2-Me-4-MeO-5-F-phenyl	H	sgl	H
140	H	2-Me-4-MeO-phenyl	H	sgl	H
141	H	2-Cl-4-CF ₃ O-phenyl	H	sgl	H

Table 2A cont.

Ex#	R7	R8	R9	b	R1
142	H	2,4,5-triMe-phenyl	H	sgl	H
143	H	3-Cl-phenyl	H	sgl	H
144	H	4-Me-phenyl	H	sgl	H
145	H	2-Me-4-Cl-phenyl	H	sgl	H
146	H	2,5-diCl-phenyl	H	sgl	H
147	H	2-MeO-4-iPr-phenyl	H	sgl	H
148	H	2,6-diCl-phenyl	H	sgl	H
149	H	2,6-diF-phenyl	H	sgl	H
150	H	2-CF ₃ -4-MeO-phenyl	H	sgl	H
151	H	2-CF ₃ -phenyl	H	sgl	H
152	H	4-pyridyl	H	sgl	H
153	H	2-furanyl	H	sgl	H
154	H	2-thiophenyl	H	sgl	H
155	H	4-F-phenyl	H	sgl	H
156	H	2,3-diCl-phenyl	H	sgl	H
157	H	4-Et-phenyl	H	sgl	H
158	H	2,4-diMeO-phenyl	H	sgl	H
159	H	2-F-3-Cl-phenyl	H	sgl	H
160	H	4-MeO-phenyl	H	sgl	H
161	H	4-MeS-phenyl	H	sgl	H
162	H	4-CN-phenyl	H	sgl	H
163	H	3-CF ₃ -phenyl	H	sgl	H
164	H	2-MeO-phenyl	H	sgl	H
165	H	2-naphthyl	H	sgl	H
166	H	4-acetylphenyl	H	sgl	H
167	H	3-acetamidophenyl	H	sgl	H
168	H	2,4-diCl-phenyl	H	sgl	Me
316	H	2,3-diMe-phenyl	H	sgl	H
317	H	2-Me-5-F-phenyl	H	sgl	H
318	H	2-F-5-Me-phenyl	H	sgl	H
319	H	2-MeO-5-F-phenyl	H	sgl	H
320	H	2-Me-3-Cl-phenyl	H	sgl	H
321	H	3-NO ₂ -phenyl	H	sgl	H
322	H	2-NO ₂ -phenyl	H	sgl	H
323	H	2-Cl-3-Me-phenyl	H	sgl	H
324	H	2-MeO-phenyl	H	sgl	H
325	H	2,3-diCl-phenyl	H	sgl	H

Table 2A cont.

Ex#	R7	R8	R9	b	R1
326	H	2-Cl-4-CF ₃ -phenyl	H	sgl	H
327	H	2-Me-4-EtO-phenyl	H	sgl	H
328	H	2-Me-4-F-phenyl	H	sgl	H
329	H	4-Bu-phenyl	H	sgl	H
330	H	2-CF ₃ -phenyl	H	sgl	H
331	H	2-Cl-6-F-phenyl	H	sgl	H
332	H	2-Cl-4-(CHF ₂)O-phenyl	H	sgl	H
333	H	4-CF ₃ -phenyl	H	sgl	H
334	H	4-Me-phenyl	H	sgl	H
335	H	4-CF ₃ O-phenyl	H	sgl	H
336	H	2,4-diMeO-6-F-phenyl	H	sgl	H
337	H	2-Me-phenyl	H	sgl	H
338	H	2-CF ₃ -6-F-phenyl	H	sgl	H
339	H	2-MeS-phenyl	H	sgl	H
340	H	2,4,6-triF-phenyl	H	sgl	H
341	H	2,4,6-triCl-phenyl	H	sgl	H
342	H	2,6-diCl-4-MeO-phenyl	H	sgl	H
343	H	2,3,4-triF-phenyl	H	sgl	H
344	H	2,6-diF-4-Cl-phenyl	H	sgl	H
345	H	2,3,4,6-tetraF-phenyl	H	sgl	H
346	H	2,3,4,5,6-pentaF-phenyl	H	sgl	H
347	H	2,6-diCF ₃ -phenyl	H	sgl	H
348	H	2-CF ₃ O-phenyl	H	sgl	H
349	H	2-CF ₃ -4-EtO-phenyl	H	sgl	H

Table 2A cont.

Ex#	R7	R8	R9	b	R1
350	H	2-CF ₃ -4-iPrO-phenyl	H	sgl	H
351	H	2-naphtyl	H	sgl	H
352	H	2-CF ₃ -4-Cl-phenyl	H	sgl	H
353	H	2-CF ₃ -4-F-phenyl	H	sgl	H
354	H	2,4-diF-phenyl	H	sgl	Me
380	H	2-Cl-4-EtO-phenyl	H	sgl	H
381	H	2-Cl-4-iPrO-phenyl	H	sgl	H
382	H	2-Et-4-MeO-phenyl	H	sgl	H
383	H	2-CHO-4-MeO-phenyl	H	sgl	H
384	H	2-CH(OH)Me-4-MeO-phenyl	H	sgl	H
385	H	2-CH(OMe)Me-4-MeO-phenyl	H	sgl	H
386	H	2-C(=O)Me-4-MeO-phenyl	H	sgl	H
387	H	2-CH ₂ (OH)-4-MeO-phenyl	H	sgl	H
388	H	2-CH ₂ (OMe)-4-MeO-phenyl	H	sgl	H
389	H	2-CH(OH)Et-4-MeO-phenyl	H	sgl	H
390	H	2-C(=O)Et-4-MeO-phenyl	H	sgl	H
391	H	(Z)-2-CH=CHCO ₂ Me-4-MeO-phenyl	H	sgl	H
392	H	2-CH ₂ CH ₂ CO ₂ Me-4-MeO-phenyl	H	sgl	H

Table 2A cont.

Ex#	R7	R8	R9	b	R1
393	H	(Z)-2-CH=CHCH ₂ (OH)- 4-MeO-phenyl	H	sgl	H
394	H	(E)-2-CH=CHCO ₂ Me-4- MeO-phenyl	H	sgl	H
395	H	(E)-2-CH=CHCH ₂ (OH)- 4-MeO-phenyl	H	sgl	H
396	H	2-CH ₂ CH ₂ OMe-4-MeO- phenyl	H	sgl	H
397	H	2-F-4-MeO-phenyl	H	sgl	H
403	H	2-Cl-4-F-phenyl	H	sgl	H
405	H	(2-Cl-phenyl)- CH=CH-	H	sgl	H
406	H	(3-Cl-phenyl)- CH=CH-	H	sgl	H
407	H	(2,6-diF-phenyl)- CH=CH-	H	sgl	H
410	H	cyclohexyl	H	sgl	H
411	H	cyclopentyl	H	sgl	H
412	H	cyclohexylmethyl	H	sgl	H
413	H	-CH ₂ CH ₂ CO ₂ Et	H	sgl	H
414	H	-(CH ₂) ₃ CO ₂ Et	H	sgl	H
415	H	-(CH ₂) ₄ CO ₂ Et	H	sgl	H
416	H	-CH ₂ CH=CH ₂	H	sgl	H
417	H	Pr	H	sgl	H
418	H	benzyl	H	sgl	H
419	H	2-F-benzyl	H	sgl	H
420	H	3-F-benzyl	H	sgl	H
421	H	4-F-benzyl	H	sgl	H
422	H	3-MeO-benzyl	H	sgl	H

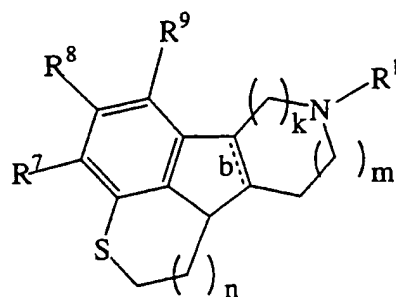
Table 2A cont.

Ex#	R7	R8	R9	b	R1
423	H	3-OH-benzyl	H	sgl	H
424	H	2-MeO-benzyl	H	sgl	H
425	H	2-OH-benzyl	H	sgl	H
426	H	2-CO ₂ Me-3-MeO- phenyl	H	sgl	H
427	H	2,6-diF-phenyl	H	sgl	H
428	H	phenyl-CH=CH-	H	sgl	H
429	H	(2-Me-4-MeO- phenyl)-CH=CH-	H	sgl	H
430	H	-NMe ₂	H	sgl	H
431	H	1-pyrrolidinyl	H	sgl	H
432	H	-NTs ₂	H	sgl	H
433	H	MeO	H	sgl	H
445	H	2-Me-4-MeO-phenyl	Me	sgl	H
446	H	2-CF ₃ -4-MeO-phenyl	Me	sgl	H
458	Me	2-CF ₃ -4-MeO-phenyl	H	sgl	H
459	Me	2,4-diCl-phenyl	H	sgl	H
460	H	3-CN-phenyl	H	sgl	H
461	H	2-Me-4-CN-phenyl	H	sgl	H
462	H	2-Me-3-CN-phenyl	H	sgl	H
463	H	2-CN-phenyl	H	sgl	H
464	H	2-CF ₃ -4-CN-phenyl	Me	sgl	H
465	H	3-CHO-phenyl	Me	sgl	H
466	H	3-CH ₂ (OH)-phenyl	Me	sgl	H
467	H	3-CH ₂ (OMe)-phenyl	Me	sgl	H
468	H	3-CH ₂ (NMe ₂)-phenyl	Me	sgl	H
469	H	3-CN-4-F-phenyl	Me	sgl	H
470	H	3-CONH ₂ -4-F-phenyl	Me	sgl	H

Table 2A cont.

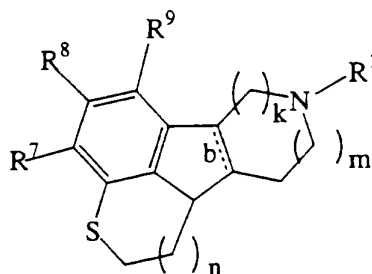
Ex#	R7	R8	R9	b	R1
580	NH ₂	H	H	sgl	H
581	H	phenyl-NH-	H	sgl	H
582	phenyl-NH-	H	H	sgl	H
583	H	(4-F-phenyl)-NH-	H	sgl	H
584	H	(2,4-diCl-phenyl)-NH-	H	sgl	H
585	H	phenyl-C(=O)NH-	H	sgl	H
586	H	benzyl-NH-	H	sgl	H
587	H	phenyl-S-	H	sgl	H
588	MeO	H	H	sgl	H
589	H	2-CH ₂ (NH ₂)-4-MeO-phenyl-	H	sgl	H
590	H	2-Me-4-MeO-phenyl-	H	sgl	H
592	H	(2-Me-4-MeO-phenyl)-NH-	H	sgl	H
593	H	(2-F-4-MeO-phenyl)-NH-	H	sgl	H
595	H	(2-Me-4-F-phenyl)-NH-	H	sgl	H

Table 3



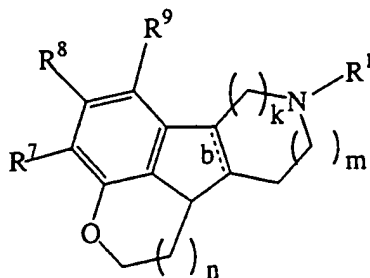
Ex#	n	k	m	R7	R8	R9	b	R1
471	2	2	1	H	H	H	sgl	H
472	2	2	1	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
473	2	2	1	H	H	H	sgl	-(CH ₂) ₃ O(4-F-phenyl)
474	2	2	1	H	H	H	sgl	-(CH ₂) ₃ (6-F-benzisoxazol-3-yl)
475	2	2	1	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-pyridyl)
476	2	3	0	H	H	H	sgl	H
477	2	3	0	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
478	2	3	0	H	H	H	sgl	-(CH ₂) ₂ (6-F-benzisoxazol-3-yl)
483	2	2	1	H	Br	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
484	2	2	1	H	Br	H	sgl	-(CH ₂) ₃ O(4-F-phenyl)
488	1	2	1	H	Br	H	sgl	-CO ₂ -tBu

Table 3A



Ex#	n	k	m	R7	R8	R9	b	R1
479	2	2	1	H	2,4-diCl-phenyl	H	sgl	H
480	2	2	1	H	2-Cl-4-MeO-phenyl	H	sgl	H
481	2	2	1	H	2-Me-4-MeO-phenyl	H	sgl	H
482	2	2	1	H	Br	H	sgl	H
497	1	1	1	H	2-Cl-phenyl	H	sgl	H
498	1	1	1	H	3-Cl-phenyl	H	sgl	H
499	1	1	1	H	3-F-phenyl	H	sgl	H
500	1	1	1	H	4-Cl-phenyl	H	sgl	H
501	1	1	1	H	4-F-phenyl	H	sgl	H
502	1	1	1	H	2,3-diCl-phenyl	H	sgl	H
503	1	1	1	H	2,3-diF-phenyl	H	sgl	H
504	1	1	1	H	3,5-diCl-phenyl	H	sgl	H
505	1	1	1	H	3,5-diF-phenyl	H	sgl	H
506	1	1	1	H	3,4-diCl-phenyl	H	sgl	H
507	1	1	1	H	3,4-diF-phenyl	H	sgl	H
508	1	1	1	H	3-Cl-4-F-phenyl	H	sgl	H
509	1	1	1	H	2-F-4-Cl-phenyl	H	sgl	H

Table 4



Ex#	n	k	m	R7	R8	R9	b	R1
172	2	1	1	H	H	H	sgl	H
173	1	1	1	H	2,4-diCl-phenyl	H	sgl	H
174	1	1	1	H	2-Cl-4-MeO-phenyl	H	sgl	H
436	1	1	1	H	2-Cl-phenyl	H	sgl	H
497	1	1	1	H	2-Cl-phenyl	H	sgl	H
498	1	1	1	H	3-Cl-phenyl	H	sgl	H
499	1	1	1	H	3-F-phenyl	H	sgl	H
500	1	1	1	H	4-Cl-phenyl	H	sgl	H
501	1	1	1	H	4-F-phenyl	H	sgl	H
502	1	1	1	H	2,3-diCl-phenyl	H	sgl	H
503	1	1	1	H	2,3-diF-phenyl	H	sgl	H
504	1	1	1	H	3,5-diCl-phenyl	H	sgl	H
505	1	1	1	H	3,5-diF-phenyl	H	sgl	H
506	1	1	1	H	3,4-diCl-phenyl	H	sgl	H
507	1	1	1	H	3,4-diF-phenyl	H	sgl	H
508	1	1	1	H	3-Cl-4-F-phenyl	H	sgl	H
509	1	1	1	H	2-F-4-Cl-phenyl	H	sgl	H
510	1	1	1	H	2-Cl-4-F-phenyl	H	sgl	H
511	1	1	1	H	2,5-diCl-phenyl	H	sgl	H
512	1	1	1	H	2,6-diCl-phenyl	H	sgl	H
513	1	1	1	H	2-CF ₃ -phenyl	H	sgl	H
514	1	1	1	H	4-CF ₃ -phenyl	H	sgl	H
515	1	1	1	H	2,4-diCF ₃ -phenyl	H	sgl	H
516	1	1	1	H	2-Cl-4-CF ₃ -phenyl	H	sgl	H
517	1	1	1	H	2-MeO-phenyl	H	sgl	H
518	1	1	1	H	2,4-diMeO-phenyl	H	sgl	H
519	1	1	1	H	2-MeO-5-iPr-phenyl	H	sgl	H
520	1	1	1	H	3-NO ₂ -phenyl	H	sgl	H
521	1	1	1	H	2-CHO-phenyl	H	sgl	H

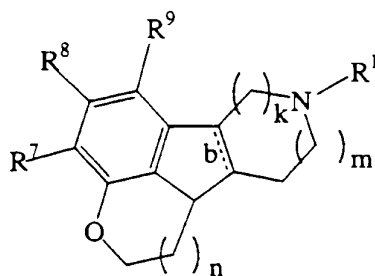
Table 4 cont.

Ex#	n	k	m	R7	R8	R9	b	R1
522	1	1	1	H	2-CH(Me) (OH) - phenyl	H	sgl	H
523	1	1	1	H	2-CH ₂ (OH) -phenyl	H	sgl	H
524	1	1	1	H	2-CHO-4-MeO-phenyl	H	sgl	H
525	1	1	1	H	2-OH-phenyl	H	sgl	H
526	1	1	1	H	2-CF ₃ -4-EtO-phenyl	H	sgl	H
527	1	1	1	H	2-CF ₃ -4-iPrO- phenyl	H	sgl	H
532	1	1	1	H	2-Me-4-MeO-phenyl	H	sgl	H
533	1	1	1	H	2-CF ₃ -4-MeO-phenyl	H	sgl	H
534	1	2	1	H	3,4,5-triMeO- phenyl	H	sgl	H
535	1	2	1	H	1-naphthyl	H	sgl	H
536	1	2	1	H	3-MeO-phenyl	H	sgl	H
537	1	2	1	H	2,4-diCl-phenyl	H	sgl	H
538	1	1	2	H	H	H	sgl	H
541	2	1	1	H	H	H	db1	H
542	2	1	1	H	H	H	sgl	H
543	2	1	1	H	2,6-diF-phenyl	H	sgl	H
545	1	2	1	H	H	H	sgl	H
547	2	1	1	H	2-CF ₃ -4-MeO-phenyl	H	sgl	H
548	2	1	1	H	2-Me-4-MeO-phenyl	H	sgl	H
549	2	1	1	H	2-Cl-4-CF ₃ -phenyl	H	sgl	H
550	2	1	1	H	2,3-diCl-phenyl	H	sgl	H
551	2	1	1	H	2,4-diMeO-phenyl	H	sgl	H
552	2	1	1	H	3,4-diMeO-phenyl	H	sgl	H
553	2	1	1	H	2,4-diCl-phenyl	H	sgl	H
554	2	1	1	H	3,4-diCl-phenyl	H	sgl	H
555	2	1	1	H	2,5-diCl-phenyl	H	sgl	H
556	2	1	1	H	2-CF ₃ -phenyl	H	sgl	H
557	2	1	1	H	2-Me-phenyl	H	sgl	H
558	2	1	1	H	2-Cl-phenyl	H	sgl	H
559	2	1	1	H	3-F-phenyl	H	sgl	H
560	2	1	1	H	phenyl	H	sgl	H

Table 4 cont.

Ex#	n	k	m	R7	R8	R9	b	R1
561	2	1	1	H	2-CF ₃ -4-EtO-phenyl	H	sgl	H
562	2	1	1	H	2-CF ₃ -4-iPrO-phenyl	H	sgl	H
563	2	1	1	H	2-MeO-4-iPr-phenyl	H	sgl	H
564	2	1	1	H	2-F-4-Cl-phenyl	H	sgl	H
565	2	1	1	H	2-Cl-4-MeO-phenyl	H	sgl	H
566	2	1	1	H	2-CHO-phenyl	H	sgl	H
567	2	1	1	H	2-CHO-4-MeO-phenyl	H	sgl	H
568	2	1	1	H	2-CH ₂ (OH)-4-MeO-phenyl	H	sgl	H
569	2	1	1	H	2-CH ₂ (OH)-phenyl	H	sgl	H
570	2	1	1	H	2-CF ₃ -4-NHMe-phenyl	H	sgl	H
571	2	1	1	H	2-CF ₃ -4-NH ₂ -phenyl	H	sgl	H
572	2	1	1	H	2-C(=O)Me-phenyl	H	sgl	H
573	2	1	1	H	2-C(=O)Me-4-MeO-phenyl	H	sgl	H
574	2	1	1	H	2-CH(Me)(OH)-phenyl	H	sgl	H
575	2	1	1	H	2-CH(Me)(OH)-4-MeO-phenyl	H	sgl	H
576	2	1	1	H	2-CF ₃ -4-OH-phenyl	H	sgl	H
577	2	1	1	H	2-CF ₃ -4-O(C=O)Me-phenyl	H	sgl	H

Table 4A

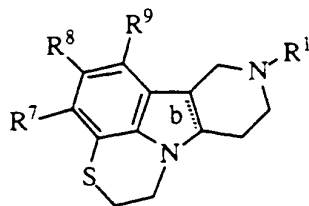


Ex#	n	k	m	R7	R8	R9	b	R1
182	1	1	1	H	H	H	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
266	1	1	1	H	H	Me	sgl	-(CH ₂) ₃ C(=O)(4-F-phenyl)
270	1	1	1	H	H	H	sgl	-(CH ₂) ₃ O(4-F-phenyl)
272	1	1	1	H	H	H	sgl	H
494	1	1	1	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NH ₂ -phenyl)
495	1	1	1	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NH ₂ -phenyl)
496	1	1	1	H	H	H	sgl	-(CH ₂) ₃ (1H-indazol-3-yl)
528	1	1	1	H	H	H	sgl	-(CH ₂) ₃ (6-F-1H-indazol-3-yl)
529	1	1	1	H	H	H	sgl	-(CH ₂) ₃ C(=O)(2-NH ₂ -4-F-phenyl)

Table 4A cont.

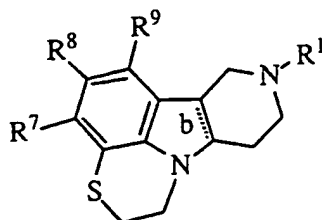
Ex#	n	k	m	R7	R8	R9	b	R1
530	1	1	1	H	H	H	sgl	$-(\text{CH}_2)_3\text{C}(=\text{O})(2\text{-NH}_2\text{-4-F-phenyl})$
531	1	1	1	H	H	H	sgl	$-(\text{CH}_2)_3\text{C}(=\text{O})(2\text{-OH-4-F-phenyl})$
539	1	2	1	H	H	H	sgl	$-(\text{CH}_2)_3\text{O}(4\text{-F-phenyl})$
540	1	2	1	H	H	H	sgl	$-(\text{CH}_2)_3(6\text{-F-1,2-benzisoxazol-3-yl})$
544	2	1	1	H	H	H	sgl	$-(\text{CH}_2)_3\text{C}(=\text{O})(4\text{-F-phenyl})$
546	1	2	1	H	H	H	sgl	$-(\text{CH}_2)_3\text{C}(=\text{O})(4\text{-F-phenyl})$

Table 5



5

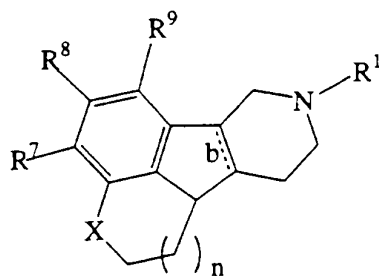
Ex#	R7	R8	R9	b	R1
183	H	H	CF ₃	dbl	-(CH ₂) ₃ CH(OH) (4-F-phenyl)
184	H	H	CF ₃	dbl	-(CH ₂) ₃ C(OCH ₂ CH ₂ O) (4-F-phenyl)
185	H	H	CF ₃	sgl	-(CH ₂) ₄ (4-F-phenyl)
188	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
195	H	H	CF ₃	dbl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
213	H	CH ₃	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
438	H	H	H	sgl	-(CH ₂) ₃ C(=O) (2-NH ₂ -phenyl)
439	H	H	H	sgl	-(CH ₂) ₃ C(=O) (2-NH ₂ -phenyl)
440	H	H	H	sgl	-(CH ₂) ₃ C(=O) (2-NH ₂ -4-F-phenyl)
441	H	H	H	sgl	-(CH ₂) ₃ C(=O) (2-NH ₂ -4-F-phenyl)
456	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
457	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)

Table 5A

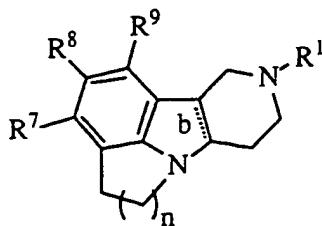
Ex#	R7	R8	R9	b	R1
443	2,3-diCl-phenyl	H	H	sgl	H
444	2,3-diF-phenyl	H	H	sgl	H
447	2,6-diCl-phenyl	H	H	sgl	H
452	2-Me-4-MeO-phenyl	H	H	sgl	H
453	2-Cl-6-F-phenyl	H	H	sgl	H
454	2,6-diF-phenyl	H	H	sgl	H
455	2,4-diCl-phenyl	H	H	sgl	H

5

Table 6



Ex#	X	n	R7	R8	R9	b	R1
398	SO ₂	2	H	2,4-diCl-phenyl	H	sgl	H
399	SO ₂	2	H	2,6-diF-phenyl	H	sgl	H
400	SO ₂	2	H	2-Cl-phenyl	H	sgl	H
401	SO ₂	2	H	2-F-4-MeO-phenyl	H	sgl	H
402	SO ₂	2	H	2-Me-4-MeO-phenyl	H	sgl	H
404	SO	2	H	2-Cl-4-F-phenyl	H	sgl	H
434	SO	2	H	2,4-diCl-phenyl	H	sgl	H
435	SO	2	H	2-Me-4-MeO-phenyl	H	sgl	H
448	SO ₂	1	H	H	H	sgl	H
449	SO	1	H	H	H	sgl	H
450	SO ₂	1	H	2-CF ₃ -4-MeO-phenyl	H	sgl	H
451	SO ₂	1	H	2,4-diCl-phenyl	H	sgl	H

Table 7

Ex#	n	R7	R8	R9	b	R1
1	1	H	H	H	dbl	H
2	1	H	H	H	dbl	cycPropyl
3	1	H	H	H	sgl	H
16	2	H	H	H	dbl	H
17	2	H	H	H	sgl	H
37	1	H	H	H	sgl	-C(=O) cycPropyl
38	1	H	H	H	sgl	-C(=O) iPropyl
89	1	H	2-Cl-phenyl	H	sgl	-CO ₂ -tButyl
90	1	H	2,4-diCl-phenyl	H	sgl	-CO ₂ -tButyl
91	1	H	3,4-diCl-phenyl	H	sgl	-CO ₂ -tButyl
92	1	H	2,3-diCl-phenyl	H	sgl	-CO ₂ -tButyl
93	1	H	2-Cl-4-CF ₃ -phenyl	H	sgl	-CO ₂ -tButyl
94	1	H	2-Cl-4-MeO-phenyl	H	sgl	-CO ₂ -tButyl
95	1	H	2-MeO-4-iPr-phenyl	H	sgl	-CO ₂ -tButyl
96	1	H	3-F-phenyl	H	sgl	-CO ₂ -tButyl
97	1	H	2,4-diMeO-phenyl	H	sgl	-CO ₂ -tButyl
98	1	H	2-Cl-phenyl	H	sgl	H
99	1	H	2,4-diCl-phenyl	H	sgl	H
100	1	H	3,4-diCl-phenyl	H	sgl	H
101	1	H	2,3-diCl-phenyl	H	sgl	H
102	1	H	2-Cl-4-CF ₃ -phenyl	H	sgl	H
103	1	H	2-Cl-4-MeO-phenyl	H	sgl	H
104	1	H	2-MeO-4-iPr-phenyl	H	sgl	H
105	1	H	3-F-phenyl	H	sgl	H
106	1	H	2,4-diMeO-phenyl	H	sgl	H
107	2	H	H	H	sgl	-CO ₂ -tButyl
108	2	H	Br	H	sgl	-CO ₂ -tButyl
109	2	H	2,3-diCl-phenyl	H	sgl	-CO ₂ -tButyl

Table 7 cont.

Ex#	n	R7	R8	R9	b	R1
110	2	H	3,4-diCl-phenyl	H	sg1	-CO ₂ -tButyl
111	2	H	2-Cl-4-CF ₃ -phenyl	H	sg1	-CO ₂ -tButyl
112	2	H	2,3-diCl-phenyl	H	sg1	H
113	2	H	3,4-diCl-phenyl	H	sg1	H
114	2	H	2-Cl-4-CF ₃ -phenyl	H	sg1	H
189	1	H	2-Cl-phenyl	H	sg1	-(CH ₂) ₃ C(=O) (4-F-phenyl)
190	1	H	2,4-diCl-phenyl	H	sg1	-(CH ₂) ₃ C(=O) (4-F-phenyl)
191	2	H	H	H	sg1	-(CH ₂) ₃ C(=O) (4-F-phenyl)
265	1	H	H	H	sg1	-(CH ₂) ₃ C(=O) (4-F-phenyl)
C274	1	H	2-F-4-MeO-phenyl	H	sg1	H
C275	1	H	2-CF ₃ -4-EtO-phenyl	H	sg1	-CO ₂ -tButyl
C276	1	H	2-CF ₃ -4-EtO-phenyl	H	sg1	H
C277	1	H	2-F-4-Cl-phenyl	H	sg1	-CO ₂ -tButyl
C278	1	H	2-F-4-Cl-phenyl	H	sg1	H
C279	1	H	2-CF ₃ -4-iPrO-phenyl	H	sg1	-CO ₂ -tButyl
C280	1	H	2-CF ₃ -4-iPrO-phenyl	H	sg1	H
C281	1	H	2-CF ₃ -4-MeO-phenyl	H	sg1	-CO ₂ -tButyl
C282	1	H	2-CF ₃ -4-MeO-phenyl	H	sg1	H
C283	1	H	phenyl	H	sg1	-CO ₂ -tButyl
284	1	H	phenyl	H	sg1	H
285	1	H	2-Me-phenyl	H	sg1	-CO ₂ -tButyl
286	1	H	2-Me-phenyl	H	sg1	H
287	1	H	2-CF ₃ -phenyl	H	sg1	-CO ₂ -tButyl
288	1	H	2-CF ₃ -phenyl	H	sg1	H
289	1	H	3,4-diMeO-phenyl	H	sg1	-CO ₂ -tButyl
290	1	H	3,4-diMeO-phenyl	H	sg1	H
291	1	H	2,5-diCl-phenyl	H	sg1	-CO ₂ -tButyl
292	1	H	2,5-diCl-phenyl	H	sg1	H
293	1	H	3,5-diCl-phenyl	H	sg1	-CO ₂ -tButyl
294	1	H	3,5-diCl-phenyl	H	sg1	H

Table 7 cont.

Ex#	n	R7	R8	R9	b	R1
295	1	H	2-iPr-4-MeO-phenyl	H	sg1	-CO ₂ -tButyl
296	1	H	2-iPr-4-MeO-phenyl	H	sg1	H
297	1	H	2-Me-4-MeO-5-F-phenyl	H	sg1	-CO ₂ -tButyl
298	1	H	2-Me-4-MeO-5-F-phenyl	H	sg1	H
299	1	H	2-Me-4-MeO-phenyl	H	sg1	-CO ₂ -tButyl
300	1	H	2-Me-4-MeO-phenyl	H	sg1	H
301	1	H	2-Cl-4-MeO-phenyl	H	sg1	-CO ₂ -tButyl
302	1	H	2-Cl-4-MeO-phenyl	H	sg1	H
303	1	H	2-Me-4-Cl-phenyl	H	sg1	-CO ₂ -tButyl
304	1	H	2-Me-4-Cl-phenyl	H	sg1	H
305	1	H	2-CHO-4-MeO-phenyl	H	sg1	H
306	1	H	2,6-diCl-phenyl	H	sg1	H
307	1	H	2-CF ₃ -4-MeNH-phenyl	H	sg1	H
308	1	H	2-CF ₃ -4-NH ₂ -phenyl	H	sg1	H
309	1	H	2-CH ₃ CH(OH)-4-MeO-phenyl	H	sg1	H
310	3	H	H	H	sg1	H
311	3	H	H	H	sg1	-CO ₂ -tButyl
312	3	H	H	H	sg1	H
313	3	H	H	H	sg1	H
314	3	H	Br	H	sg1	-CO ₂ -tButyl
315	3	H	2,4-diCl-phenyl	H	sg1	H
316	3	H	2,3-diCl-phenyl	H	sg1	H
317	3	H	3,4-diCl-phenyl	H	sg1	H
318	3	H	3,5-diCl-phenyl	H	sg1	H
319	3	H	2,5-diCl-phenyl	H	sg1	H
320	3	H	2,6-diCl-phenyl	H	sg1	H
321	3	H	2-Cl-phenyl	H	sg1	H
322	3	H	3-Cl-phenyl	H	sg1	H
323	3	H	4-Cl-phenyl	H	sg1	H
324	3	H	2,6-diF-phenyl	H	sg1	H
325	3	H	2,6-diF-phenyl	H	sg1	H
326	3	H	2,3-diF-phenyl	H	sg1	H
327	3	H	3,4-diF-phenyl	H	sg1	H

Table 7 cont.

Ex#	n	R7	R8	R9	b	R1
328	3	H	3-F-phenyl	H	sgl	H
329	3	H	2-Cl-4-CF ₃ -phenyl	H	sgl	H
330	3	H	2-Cl-4-MeO-phenyl	H	sgl	H
331	3	H	2-F-4-MeO-phenyl	H	sgl	H
332	3	H	2-Me-4-MeO-phenyl	H	sgl	H
333	3	H	2-CF ₃ -4-MeO-phenyl	H	sgl	H
334	3	H	2-CF ₃ -phenyl	H	sgl	H
335	3	H	2-CF ₃ -4-iPrO-phenyl	H	sgl	H
336	3	H	2,4-diCF ₃ -phenyl	H	sgl	H
337	3	H	2-CF ₃ -4-F-phenyl	H	sgl	H
338	3	H	2-CF ₃ -4-NH ₂ -phenyl	H	sgl	H
339	3	H	2-CF ₃ -4-MeNH-phenyl	H	sgl	H
340	3	H	2-CHO-phenyl	H	sgl	H
341	3	H	2-CH ₂ (OH)-phenyl	H	sgl	H
342	3	H	2-CHO-4-MeO-phenyl	H	sgl	H
343	3	H	2-CH ₂ (OH)-4-MeO-phenyl	H	sgl	H
344	3	H	2-Me-4-CN-phenyl	H	sgl	H
345	3	H	2-CH ₃ CH(OH)-4-MeO-phenyl	H	sgl	H
346	2	H	Br	H	sgl	-CO ₂ -tButyl
347	2	H	2,4-diCl-phenyl	H	sgl	H
348	2	H	3,4-diCl-phenyl	H	sgl	H
349	2	H	3,5-diCl-phenyl	H	sgl	H
350	2	H	2,5-diCl-phenyl	H	sgl	H
351	2	H	2,6-diCl-phenyl	H	sgl	H
352	2	H	2-Cl-phenyl	H	sgl	H
353	2	H	3-Cl-phenyl	H	sgl	H
354	2	H	4-Cl-phenyl	H	sgl	H
355	2	H	2,6-diF-phenyl	H	sgl	H
356	2	H	2,6-diF-phenyl	H	sgl	Me
357	2	H	2,3-diF-phenyl	H	sgl	H
358	2	H	3,4-diF-phenyl	H	sgl	H
359	2	H	3-F-phenyl	H	sgl	H
360	2	H	2-Cl-4-MeO-phenyl	H	sgl	H

Table 7 cont.

Ex#	n	R7	R8	R9	b	R1
361	2	H	2-F-4-MeO-phenyl	H	sgl	H
362	2	H	2-Me-4-MeO-phenyl	H	sgl	H
363	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	H
364	2	H	2-CF ₃ -4-MeO-phenyl	H	dbl	H
365	2	H	2-CF ₃ -4-OH-phenyl	H	sgl	H
366	2	H	2-CF ₃ -phenyl	H	sgl	H
367	2	H	2-CF ₃ -4-iPrO-phenyl	H	sgl	H
368	2	H	2,4-diCF ₃ -phenyl	H	sgl	H
369	2	H	2-CF ₃ -4-F-phenyl	H	sgl	H
370	2	H	2-CF ₃ -4-NH ₂ -phenyl	H	sgl	H
371	2	H	2-CF ₃ -4-MeNH-phenyl	H	sgl	H
372	2	H	4-CN-2-Me-phenyl	H	sgl	H
373	2	H	2-CHO-phenyl	H	sgl	H
374	2	H	2-CH ₂ (OH)-phenyl	H	sgl	H
375	2	H	2-CHO-4-MeO-phenyl	H	sgl	H
376	2	H	2-CH ₂ (OH)-4-MeO-phenyl	H	sgl	H
377	3	H	2-CF ₃ -4-EtO-phenyl	H	sgl	H
378	2	H	2-CF ₃ -4-EtO-phenyl	H	sgl	H
379	3	H	2-Me-3-Cl-phenyl	H	sgl	H
380	2	H	2-Me-3-Cl-phenyl	H	sgl	H
381	2	H	2-Me-5-F-phenyl	H	sgl	H
382	2	H	2,3-diCl-phenyl	H	sgl	Pr
383	2	H	2,3-diCl-phenyl	H	sgl	Pr
384	2	H	2,3-diCl-phenyl	H	sgl	Bu
385	2	H	2,3-diCl-phenyl	H	sgl	Bu
386	2	H	2,3-diCl-phenyl	H	sgl	4-pentenyl
387	2	H	2,3-diCl-phenyl	H	sgl	3-Me-2-butenyl
388	2	H	2,4-diCl-phenyl	H	sgl	Pr
389	2	H	2,4-diCl-phenyl	H	sgl	Bu
390	2	H	2,4-diCl-phenyl	H	sgl	4-pentenyl
391	2	H	2,4-diCl-phenyl	H	sgl	3-Me-2-butenyl
392	2	H	2,4-diCl-phenyl	H	sgl	cyclobutylmethyl
393	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	Me
394	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	Et

Table 7 cont.

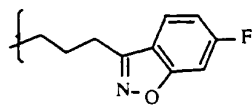
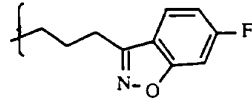
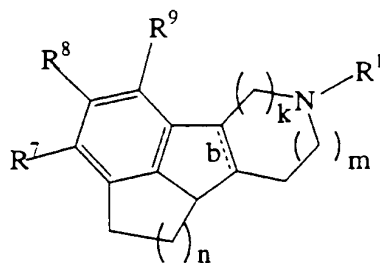
Ex#	n	R7	R8	R9	b	R1
395	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	Pr
396	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	Bu
397	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	4-pentenyl
398	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	3-Me-2-butenyl
399	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	2-F-ethyl
400	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	2,2-diF-ethyl
401	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	cyclobutylmethyl
402	2	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
403	2	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
403	2	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
404	2	H	H	H	sgl	-(CH ₂) ₃ C(=O) (2-NH ₂ -phenyl)
405	2	H	H	H	sgl	-(CH ₂) ₃ C(=O) (2-NH ₂ -phenyl)
406	2	H	H	H	sgl	-(CH ₂) ₃ O (4-F-phenyl)
407	2	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-pyridyl)
408	2	H	H	H	sgl	
409	2	H	H	H	sgl	
410	2	H	H	H	dbl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
411	3	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
412	3	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)

Table 7 cont.

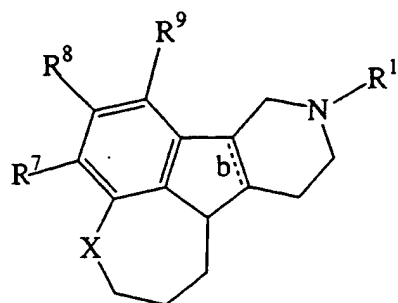
Ex#	n	R7	R8	R9	b	R1
413	3	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
414	3	H	H	H	sgl	-(CH ₂) ₃ C(=O) (2-NH ₂ -4-F-phenyl)
415	2	H	H	H	sgl	-(CH ₂) ₃ C(=O) (2-NH ₂ -4-F-phenyl)
416	2	H	H	H	sgl	-(CH ₂) ₃ C(=O) (2-NH ₂ -4-F-phenyl)
417	2	H	H	H	sgl	-(CH ₂) ₃ C(=O) (2-NH ₂ -4-F-phenyl)

Table 8



Ex#	n	k	m	R7	R8	R9	b	R1
418	2	2	1	H	H	H	dbl	H
419	2	2	1	H	H	H	sgl	H
420	2	2	1	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
421	2	2	1	H	H	H	sgl	-(CH ₂) ₃ C(=O) (2-NH ₂ -4-F-phenyl)
422	3	2	1	H	H	H	dbl	H
423	3	2	1	H	H	H	sgl	H
424	3	2	1	H	H	H	sgl	-(CH ₂) ₃ C(=O) (4-F-phenyl)
425	3	2	1	H	H	H	sgl	-(CH ₂) ₃ C(=O) (2-NH ₂ -4-F-phenyl)
434	2	1	2	H	H	H	sgl	H
435	2	1	2	H	H	H	sgl	-CO ₂ -tButyl
436	2	1	2	H	Br	H	sgl	-CO ₂ -tButyl
437	2	1	2	H	2-CF ₃ -4-MeO-phenyl	H	sgl	H

Table 9

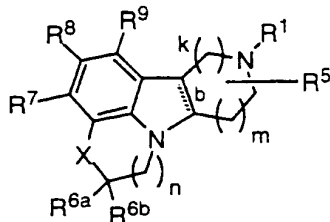


Ex#	X	R7	R8	R9	b	R1
426	C=O	H	H	H	sg1	H
427	C=O	H	H	H	sg1	-CO ₂ -tButyl
428	C=O	H	2,4-diCl-phenyl	H	sg1	-CO ₂ -tButyl
429	C=O	H	2,4-diCl-phenyl	H	sg1	H
430	C=O	H	2,4-diCl-phenyl	H	sg1	H
431	C=O	H	2,4-diCl-phenyl	H	sg1	H
432	CH(OH)	H	2,4-diCl-phenyl	H	sg1	H
433	CH(OH)	H	2,4-diCl-phenyl	H	sg1	H

CLAIMS

What is claimed is:

- 5 1. A compound of the formula (I):



(I)

or stereoisomers or pharmaceutically acceptable salt forms
 10 thereof, wherein:

b is a single bond or a double bond;

X is -NR^{10A}-, -C(=O)NR^{10A}-, or -NR^{10A}C(=O)-;
 15

R¹ is selected from

- H,
- C(=O)R²,
- C(=O)OR²,
- 20 C₁₋₈ alkyl,
- C₂₋₈ alkenyl,
- C₂₋₈ alkynyl,
- C₃₋₇ cycloalkyl,
- C₁₋₆ alkyl substituted with Z,
- 25 C₂₋₆ alkenyl substituted with Z,
- C₂₋₆ alkynyl substituted with Z,
- C₃₋₆ cycloalkyl substituted with Z,
- aryl substituted with Z,
- 5-6 membered heterocyclic ring system containing at
 30 least one heteroatom selected from the group

- consisting of N, O, and S, said heterocyclic ring system substituted with Z;
- C₁₋₃ alkyl substituted with Y,
- C₂₋₃ alkenyl substituted with Y,
- 5 C₂₋₃ alkynyl substituted with Y,
- C₁₋₆ alkyl substituted with 0-2 R²,
- C₂₋₆ alkenyl substituted with 0-2 R²,
- C₂₋₆ alkynyl substituted with 0-2 R²,
- aryl substituted with 0-2 R², and
- 10 5-6 membered heterocyclic ring system containing at least one heteroatom selected from the group consisting of N, O, and S, said heterocyclic ring system substituted with 0-2 R²;
- 15 Y is selected from
- C₃₋₆ cycloalkyl substituted with Z,
- aryl substituted with Z,
- 5-6 membered heterocyclic ring system containing at least one heteroatom selected from the group
- 20 consisting of N, O, and S, said heterocyclic ring system substituted with Z;
- C₃₋₆ cycloalkyl substituted with -(C₁₋₃ alkyl)-Z,
- aryl substituted with -(C₁₋₃ alkyl)-Z, and
- 5-6 membered heterocyclic ring system containing at least one heteroatom selected from the group
- 25 consisting of N, O, and S, said heterocyclic ring system substituted with -(C₁₋₃ alkyl)-Z;
- Z is selected from H,
- 30 -CH(OH)R²,
- C(ethylenedioxy)R²,
- OR²,
- SR²,
- NR²R³,

- C(O)R²,
-C(O)NR²R³,
-NR³C(O)R²,
-C(O)OR²,
5 -OC(O)R²,
-CH(=NR⁴)NR²R³,
-NHC(=NR⁴)NR²R³,
-S(O)R²,
-S(O)₂R²,
10 -S(O)₂NR²R³, and -NR³S(O)₂R²;

- R², at each occurrence, is independently selected from
halo,
C₁₋₃ haloalkyl,
15 C₁₋₄ alkyl,
C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
aryl substituted with 0-5 R⁴²;
20 C₃₋₁₀ carbocyclic residue substituted with 0-3 R⁴¹, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴¹;

- 25 R³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, and
C₁₋₄ alkoxy;

- 30 alternatively, R² and R³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R⁴)-;

R⁴, at each occurrence, is independently selected from H and C₁₋₄ alkyl;

R⁵ is H or C₁₋₄ alkyl;

5

R^{6a} and R^{6b}, at each occurrence, are independently selected from

H, -OH, -NR⁴⁶R⁴⁷, -CF₃, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl,

10

and
aryl substituted with 0-3 R⁴⁴;

R⁷ and R⁹, at each occurrence, are independently selected from

15

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,
C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl,
C₁₋₈ alkoxy, (C₁₋₄ haloalkyl)oxy,

C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,

C₁₋₄ alkyl substituted with 0-2 R¹¹,

20

C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,

aryl substituted with 0-5 R³³,

5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group

consisting of N, O, and S substituted with 0-3

25

R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,

NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,

CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹²,

30

S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹²,

NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and

NR¹²C(O)NHR¹⁵;

R⁸ is selected from

- H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂,
C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl,
C₁₋₈ alkoxy, (C₁₋₄ haloalkyl)oxy,
5 C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
C₁₋₄ alkyl substituted with 0-2 R¹¹,
C₂₋₄ alkenyl substituted with 0-2 R¹¹,
C₂₋₄ alkynyl substituted with 0-1 R¹¹,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
10 aryl substituted with 0-5 R³³,
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;
15
OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,
CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹²,
S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹²,
20 NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and
NR¹²C(O)NHR¹⁵;

R^{10A} is selected from H,

- C₁₋₆ alkyl substituted with 0-1 R^{10B},
25 C₂₋₆ alkenyl substituted with 0-1 R^{10B},
C₂₋₆ alkynyl substituted with 0-1 R^{10B}, and
C₁₋₆ alkoxy;

R^{10B} is selected from

- 30 C₁₋₄ alkoxy,
C₃₋₆ cycloalkyl,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
phenyl substituted with 0-3 R³³, and

5-6 membered heterocyclic ring system containing 1, 2,
or 3 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-2
R⁴⁴;

5

R¹¹ is selected from

H, halo, -CF₃, -CN, -NO₂,

C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl,

C₁₋₈ alkoxy, C₃₋₁₀ cycloalkyl,

10

C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,

aryl substituted with 0-5 R³³,

5-10 membered heterocyclic ring system containing from

1-4 heteroatoms selected from the group

consisting of N, O, and S substituted with 0-3

15

R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,

NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,

CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹²,

20

S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹²,

NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and

NR¹²C(O)NHR¹⁵;

R¹², at each occurrence, is independently selected from

25

C₁₋₄ alkyl substituted with 0-1 R^{12a},

C₂₋₄ alkenyl substituted with 0-1 R^{12a},

C₂₋₄ alkynyl substituted with 0-1 R^{12a},

C₃₋₆ cycloalkyl substituted with 0-3 R³³,

phenyl substituted with 0-5 R³³;

30

C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and

5-10 membered heterocyclic ring system containing from

1-4 heteroatoms selected from the group

consisting of N, O, and S substituted with 0-3
R³¹;

5 R^{12a}, at each occurrence, is independently selected from
phenyl substituted with 0-5 R³³;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
10 R³¹;

R¹³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

15 alternatively, R¹² and R¹³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R¹⁴)-;

alternatively, R¹² and R¹³ when attached to N may be
combined to form a 9- or 10-membered bicyclic
20 heterocyclic ring system containing from 1-3
heteroatoms selected from the group consisting of N,
O, and S, wherein said bicyclic heterocyclic ring
system is unsaturated or partially saturated, wherein
said bicyclic heterocyclic ring system is substituted
25 with 0-3 R¹⁶;

R¹⁴, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;

30 R¹⁵, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

R¹⁶, at each occurrence, is independently selected from
H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,

C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl, C₁₋₃ haloalkyl-oxy-, and C₁₋₃ alkyloxy-;

5 R³¹, at each occurrence, is independently selected from H, OH, halo, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, and C₁₋₄ alkyl;

10 R³³, at each occurrence, is independently selected from H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-, C₁₋₄ alkyloxy-, C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-, C₁₋₄ alkyl-OC(=O)-, C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆ cycloalkylmethyl-oxy-; 15 C₁₋₆ alkyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy; and C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy;

20 R⁴¹, at each occurrence, is independently selected from H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, =O; C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl C₁₋₄ alkyl substituted with 0-1 R⁴³, 25 aryl substituted with 0-3 R⁴², and 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-3 R⁴⁴;

30

R⁴², at each occurrence, is independently selected from

H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, SOR⁴⁵, SR⁴⁵, NR⁴⁶SO₂R⁴⁵,
NR⁴⁶COR⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, CH(=NH)NH₂,
NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
5 C₃₋₆ cycloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴⁴, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
10 consisting of N, O, and S substituted with 0-3
R⁴⁴;

R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;

15 R⁴⁴, at each occurrence, is independently selected from H,
halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂,
C₁₋₄ alkyl, and C₁₋₄ alkoxy;

R⁴⁵ is C₁₋₄ alkyl;

20

R⁴⁶, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;

R⁴⁷, at each occurrence, is independently selected from H,
25 C₁₋₄ alkyl, -C(=O)NH(C₁₋₄ alkyl), -SO₂(C₁₋₄ alkyl),
-C(=O)O(C₁₋₄ alkyl), -C(=O)(C₁₋₄ alkyl), and -C(=O)H;

k is 1 or 2;

m is 0, 1, or 2;

30 n is 1, 2, or 3;

provided when m is 0 or 1 then k is 1 or 2;

provided when m is 2 then k is 1;

provided that when $n=0$, then R^6 or R^{6a} is not NH_2 or $-OH$.

2. A compound of Claim 1 wherein:

5 X is $-NR^{10A}-$, $-C(=O)NH-$, or $-NHC(=O)-$;

R^1 is selected from

H,
C(=O) R^2 ,
10 C(=O)OR 2 ,
C₁₋₈ alkyl,
C₂₋₈ alkenyl,
C₂₋₈ alkynyl,
C₃₋₇ cycloalkyl,
15 C₁₋₆ alkyl substituted with 0-2 R^2 ,
C₂₋₆ alkenyl substituted with 0-2 R^2 ,
C₂₋₆ alkynyl substituted with 0-2 R^2 ,
aryl substituted with 0-2 R^2 , and
5-6 membered heterocyclic ring system containing at
20 least one heteroatom selected from the group
consisting of N, O, and S, said heterocyclic ring
system substituted with 0-2 R^2 ;

R^2 , at each occurrence, is independently selected from

25 F, Cl, CH_2F , CHF_2 , CF_3 ,
C₁₋₄ alkyl,
C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
30 phenyl substituted with 0-5 R^{42} ;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R^{41} , and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group

consisting of N, O, and S substituted with 0-3
R⁴¹;

R⁵ is H, methyl, ethyl, propyl, or butyl;

5

R^{6a} is selected from

H, -OH, -NR⁴⁶R⁴⁷, -CF₃,

C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, and
aryl substituted with 0-3 R⁴⁴;

10

R^{6b} is H;

R⁷ and R⁹, at each occurrence, are independently selected
from

15 H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,
C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl,
C₁₋₈ alkoxy, (C₁₋₄ haloalkyl)oxy,

C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,

C₁₋₄ alkyl substituted with 0-2 R¹¹,

20 C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³,

5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
25 R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,

NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,

CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹²,

30 S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹²,

NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and

NR¹²C(O)NHR¹⁵;

R⁸ is selected from

- H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂,
- C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl,
- C₁₋₈ alkoxy, (C₁₋₄ haloalkyl)oxy,
- 5 C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
- C₁₋₄ alkyl substituted with 0-2 R¹¹,
- C₂₋₄ alkenyl substituted with 0-2 R¹¹,
- C₂₋₄ alkynyl substituted with 0-1 R¹¹,
- C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
- 10 aryl substituted with 0-5 R³³,
- 5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;
- 15 OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
- NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,
- CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹²,
- S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹²,
- 20 NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and
- NR¹²C(O)NHR¹⁵;

R^{10A} is selected from H,

- C₁₋₆ alkyl substituted with 0-1 R^{10B},
- 25 C₂₋₆ alkenyl substituted with 0-1 R^{10B},
- C₂₋₆ alkynyl substituted with 0-1 R^{10B}, and
- C₁₋₆ alkoxy;

R^{10B} is selected from

- 30 C₁₋₄ alkoxy,
- C₃₋₆ cycloalkyl,
- C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
- phenyl substituted with 0-3 R³³, and

5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴⁴;

5

R¹¹ is selected from

H, halo, -CF₃, -CN, -NO₂,

C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, C₃₋₁₀ cycloalkyl,

10 C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, aryl substituted with 0-5 R³³, 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-3 R³¹;

15

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³, NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹², CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;

20

R¹², at each occurrence, is independently selected from

25

C₁₋₄ alkyl substituted with 0-1 R^{12a},

C₂₋₄ alkenyl substituted with 0-1 R^{12a},

C₂₋₄ alkynyl substituted with 0-1 R^{12a},

C₃₋₆ cycloalkyl substituted with 0-3 R³³,

phenyl substituted with 0-5 R³³;

30

C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms selected from the group

consisting of N, O, and S substituted with 0-3
R³¹;

5 R^{12a}, at each occurrence, is independently selected from
phenyl substituted with 0-5 R³³;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
10 R³¹;

R¹³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;
15 alternatively, R¹² and R¹³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R¹⁴)-;

alternatively, R¹² and R¹³ when attached to N may be
20 combined to form a 9- or 10-membered bicyclic
heterocyclic ring system containing from 1-3
heteroatoms selected from the group consisting of N,
O, and S, wherein said bicyclic heterocyclic ring
system is unsaturated or partially saturated, wherein
25 said bicyclic heterocyclic ring system is substituted
with 0-3 R¹⁶;

R¹⁴, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;
30

R¹⁵, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

R¹⁶, at each occurrence, is independently selected from

H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl,
C₁₋₃ haloalkyl-oxy-, and C₁₋₃ alkyloxy-;

5 R³¹, at each occurrence, is independently selected from
H, OH, halo, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, and C₁₋₄ alkyl;

R³³, at each occurrence, is independently selected from
H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
10 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-,
C₁₋₄ alkyloxy-,
C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-,
C₁₋₄ alkyl-OC(=O)-,
15 C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆
cycloalkylmethyl-oxy-;
C₁₋₆ alkyl substituted with OH, methoxy, ethoxy,
propoxy, or butoxy; and
C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy,
20 propoxy, or butoxy;

R⁴¹, at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN;
C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl
25 C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴², and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
30 R⁴⁴;

R⁴², at each occurrence, is independently selected from

H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,
CH(=NH)NH₂, NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
C₃₋₆ cycloalkyl,
5 C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴⁴, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
10 R⁴⁴;

R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;

R⁴⁴, at each occurrence, is independently selected from H,
15 halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂,
C₁₋₄ alkyl, and C₁₋₄ alkoxy;

R⁴⁵ is C₁₋₄ alkyl;

20 R⁴⁶, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;

R⁴⁷, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;

25

k is 1 or 2;

m is 0, 1, or 2; and

n is 1, 2, or 3.

30 3. A compound of Claim 2 wherein:

X is -NR^{10A}-;

R¹ is selected from

H,
C(=O)R²,
C(=O)OR²,
C₁₋₆ alkyl,
5 C₂₋₆ alkenyl,
C₂₋₆ alkynyl,
C₃₋₆ cycloalkyl,
C₁₋₄ alkyl substituted with 0-2 R²,
C₂₋₄ alkenyl substituted with 0-2 R², and
10 C₂₋₄ alkynyl substituted with 0-2 R²;

R², at each occurrence, is independently selected from
C₁₋₄ alkyl,
C₂₋₄ alkenyl,
15 C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
phenyl substituted with 0-5 R⁴²;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R⁴¹, and
5-10 membered heterocyclic ring system containing from
20 1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴¹;

R⁵ is H, methyl, ethyl, propyl, or butyl;
25

R^{6a} is selected independently from
H, -OH, -NR⁴⁶R⁴⁷, -CF₃, C₁₋₃ alkyl, and C₁₋₃ alkoxy;

R^{6b} is H;
30

R⁷ and R⁹, at each occurrence, are independently selected
from
H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,

C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl,
C₁₋₆ alkoxy, (C₁₋₄ haloalkyl)oxy,
C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
C₁₋₄ alkyl substituted with 0-2 R¹¹,
5 C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³,
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
10 R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,
CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹²,
15 S(O)₂R¹², S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹²,
and NR¹⁴S(O)₂R¹²;

R⁸ is selected from
H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂,
20 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ haloalkyl,
C₁₋₆ alkoxy, (C₁₋₄ haloalkyl)oxy,
C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
C₁₋₄ alkyl substituted with 0-2 R¹¹,
C₂₋₄ alkenyl substituted with 0-2 R¹¹,
25 C₂₋₄ alkynyl substituted with 0-1 R¹¹,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³,
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
30 consisting of N, O, and S substituted with 0-3
R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
 NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,
 CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹²,
 S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹²,
 5 NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and
 NR¹²C(O)NHR¹⁵;

R^{10A} is selected from H,

C₁₋₄ alkyl substituted with 0-1 R^{10B},
 10 C₂₋₄ alkenyl substituted with 0-1 R^{10B},
 C₂₋₄ alkynyl substituted with 0-1 R^{10B}, and
 C₁₋₆ alkoxy;

R^{10B} is selected from

15 C₁₋₄ alkoxy,
 C₃₋₆ cycloalkyl,
 phenyl substituted with 0-3 R³³, and
 5-6 membered heterocyclic ring system containing 1, 2,
 or 3 heteroatoms selected from the group
 20 consisting of N, O, and S substituted with 0-2
 R⁴⁴;

R¹¹ is selected from

H, halo, -CF₃, -CN, -NO₂, C₁₋₆ alkyl,
 25 C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl, C₁₋₆ alkoxy,
 C₃₋₁₀ cycloalkyl,
 C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
 aryl substituted with 0-5 R³³,
 5-10 membered heterocyclic ring system containing from
 30 1-4 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-3
 R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,
CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹²,
S(O)₂R¹², S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹²,
5 and NR¹⁴S(O)₂R¹²;

R¹², at each occurrence, is independently selected from
C₁₋₄ alkyl substituted with 0-1 R^{12a},
C₂₋₄ alkenyl substituted with 0-1 R^{12a},
10 C₂₋₄ alkynyl substituted with 0-1 R^{12a},
C₃₋₆ cycloalkyl substituted with 0-3 R³³,
phenyl substituted with 0-5 R³³;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and
5-10 membered heterocyclic ring system containing from
15 1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;

R^{12a}, at each occurrence, is independently selected from
20 phenyl substituted with 0-5 R³³;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
25 R³¹;

R¹³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

30 alternatively, R¹² and R¹³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R¹⁴)-;

- alternatively, R¹² and R¹³ when attached to N may be combined to form a 9- or 10-membered bicyclic heterocyclic ring system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S, wherein said bicyclic heterocyclic ring system is unsaturated or partially saturated, wherein said bicyclic heterocyclic ring system is substituted with 0-3 R¹⁶;
- 5 R¹⁴, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and butyl;
- R¹⁵, at each occurrence, is independently selected from H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;
- 15 R¹⁶, at each occurrence, is independently selected from H, OH, F, Cl, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, and trifluoromethoxy;
- 20 R³¹, at each occurrence, is independently selected from H, OH, halo, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, and C₁₋₄ alkyl;
- R³³, at each occurrence, is independently selected from
- 25 H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-, C₁₋₄ alkyloxy-, C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-,
- 30 C₁₋₄ alkyl-OC(=O)-, C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆ cycloalkylmethyl-oxy-, C₁₋₆ alkyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy; and

C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy, propoxy, or butoxy;

5 R⁴¹, at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,
C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl
C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴², and
10 5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴⁴;

R⁴², at each occurrence, is independently selected from
15 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,
CH(=NH)NH₂, NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
C₃₋₆ cycloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
20 aryl substituted with 0-3 R⁴⁴, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴⁴;

25 R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;

R⁴⁴, at each occurrence, is independently selected from H,
halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂,
30 C₁₋₄ alkyl, and C₁₋₄ alkoxy;

R⁴⁵ is C₁₋₄ alkyl;

R⁴⁶, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;

5 R⁴⁷, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;

k is 1 or 2;

m is 0 or 1; and

10

n is 1 or 2.

4. A compound of Claim 2 wherein:

15 X is -NH-;

R¹ is selected from

H,
C₁₋₄ alkyl,
20 C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
C₃₋₄ cycloalkyl,
C₁₋₃ alkyl substituted with 0-1 R²,
C₂₋₃ alkenyl substituted with 0-1 R², and
25 C₂₋₃ alkynyl substituted with 0-1 R²;

R², at each occurrence, is independently selected from

C₁₋₄ alkyl,
C₂₋₄ alkenyl,
30 C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
phenyl substituted with 0-5 R⁴²;
C₃₋₆ carbocyclic residue substituted with 0-3 R⁴¹, and

5-6 membered heterocyclic ring system containing 1, 2, or 3 heteroatoms selected from the group consisting of N, O, and S substituted with 0-3 R⁴¹;

5

R⁵ is H, methyl, ethyl, propyl, or butyl;

R^{6a} is H, methyl, ethyl, methoxy, -OH, or -CF₃;

10 R^{6b} is H;

R⁷ and R⁹, at each occurrence, are independently selected from

15 H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl,
C₁₋₄ alkoxy, (C₁₋₄ haloalkyl)oxy,
C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
C₁₋₄ alkyl substituted with 0-2 R¹¹,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
20 aryl substituted with 0-5 R³³, and
5-6 membered heterocyclic ring system containing 1, 2,
or 3 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;

25

R⁸ is selected from

H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl,
C₁₋₄ alkoxy, (C₁₋₄ haloalkyl)oxy,
30 C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
C₁₋₄ alkyl substituted with 0-2 R¹¹,
C₂₋₄ alkenyl substituted with 0-2 R¹¹,
C₂₋₄ alkynyl substituted with 0-1 R¹¹,

- C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³,
5-6 membered heterocyclic ring system containing 1, 2,
or 3 heteroatoms selected from the group
5 consisting of N, O, and S substituted with 0-3
R³¹;
OR¹², SR¹², NR¹²R¹³, NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵,
NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;
- 10 R¹¹ is selected from
H, halo, -CF₃, -CN, -NO₂,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl,
C₁₋₄ alkoxy, (C₁₋₄ haloalkyl)oxy,
C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
15 C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³, and
5-6 membered heterocyclic ring system containing 1, 2,
or 3 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
20 R³¹;
- R¹², at each occurrence, is independently selected from
C₁₋₄ alkyl substituted with 0-1 R^{12a},
C₂₋₄ alkenyl substituted with 0-1 R^{12a},
25 C₂₋₄ alkynyl substituted with 0-1 R^{12a},
C₃₋₆ cycloalkyl substituted with 0-3 R³³,
phenyl substituted with 0-5 R³³;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and
5-10 membered heterocyclic ring system containing from
30 1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;

R^{12a}, at each occurrence, is independently selected from
phenyl substituted with 0-5 R³³;
C₃-10 carbocyclic residue substituted with 0-3 R³³, and
5 5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;

R¹³, at each occurrence, is independently selected from
10 H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

alternatively, R¹² and R¹³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R¹⁴)-;

15 alternatively, R¹² and R¹³ when attached to N may be
combined to form a 9- or 10-membered bicyclic
heterocyclic ring system containing from 1-3
heteroatoms selected from the group consisting of one
N, two N, three N, one N one O, and one N one S;
20 wherein said bicyclic heterocyclic ring system is
unsaturated or partially saturated, wherein said
bicyclic heterocyclic ring system is substituted with
0-2 R¹⁶;

25 R¹⁴, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;

R¹⁵, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;

30

R¹⁶, at each occurrence, is independently selected from
H, OH, F, Cl, CN, NO₂, methyl, ethyl, methoxy, ethoxy,
trifluoromethyl, and trifluoromethoxy;

35 R³¹, at each occurrence, is independently selected from

H, OH, halo, CF₃, methyl, ethyl, and propyl;

R³³, at each occurrence, is independently selected from
H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
5 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-,
C₁₋₄ alkyloxy-,
C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-,
C₁₋₄ alkyl-OC(=O)-,
10 C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆
cycloalkylmethyl-oxy-;
C₁₋₆ alkyl substituted with OH, methoxy, ethoxy,
propoxy, or butoxy; and
C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy,
15 propoxy, or butoxy;

R⁴¹, at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,
C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl,
20 and C₁₋₃ alkyl;

R⁴², at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,
CH(=NH)NH₂, NHC(=NH)NH₂,
25 C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl,
C₃₋₆ cycloalkyl, and C₁₋₃ alkyl;

R⁴³ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
phenyl, or pyridyl, each substituted with 0-3 R⁴⁴;
30

R⁴⁴, at each occurrence, is independently selected from H,
halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂,

methyl, ethyl, propyl, butyl, methoxy, ethoxy,
propoxy, and butoxy;

R⁴⁵ is methyl, ethyl, propyl, or butyl;

5

R⁴⁶, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;

R⁴⁷, at each occurrence, is independently selected from
10 from H, methyl, ethyl, propyl, and butyl;

k is 1;

m is 1; and

15

n is 1 or 2.

5. A compound of Claim 2 wherein:

20 X is -NH-;

R¹ is selected from

H,

C₁₋₄ alkyl,

25

C₂₋₄ alkenyl,

C₂₋₄ alkynyl,

C₃₋₄ cycloalkyl,

C₁₋₃ alkyl substituted with 0-1 R²,

C₂₋₃ alkenyl substituted with 0-1 R², and

30

C₂₋₃ alkynyl substituted with 0-1 R²;

R², at each occurrence, is independently selected from

C₁₋₄ alkyl,

C₂₋₄ alkenyl,

- C₂₋₄ alkynyl,
C₃₋₆ cycloalkyl,
phenyl substituted with 0-5 R⁴²;
C₃₋₆ carbocyclic residue substituted with 0-3 R⁴¹, and
5 5-6 membered heterocyclic ring system containing 1, 2,
or 3 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴¹;
- 10 R⁵ is H, methyl, ethyl, propyl, or butyl;
- R^{6a} is H, methyl, ethyl, methoxy, -OH, or -CF₃;
- R^{6b} is H;
- 15 R⁷ and R⁹, at each occurrence, are independently selected
from
H, F, Cl, -CH₃, -OCH₃, -CF₃, -OCF₃, -CN, and -NO₂,
- 20 R⁸ is selected from
H, F, Cl, Br, -CF₃, -OCF₃, -OH, -CN, -NO₂,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl,
C₁₋₄ alkoxy, (C₁₋₄ haloalkyl)oxy,
C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
25 C₁₋₄ alkyl substituted with 0-2 R¹¹,
C₂₋₄ alkenyl substituted with 0-2 R¹¹,
C₂₋₄ alkynyl substituted with 0-1 R¹¹,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³,
30 5-6 membered heterocyclic ring system containing 1, 2,
or 3 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;

OR¹², SR¹², NR¹²R¹³, NR¹²C(O)R¹⁵, NR¹²C(O)OR¹⁵,
NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;

R¹¹ is selected from

5 H, halo, -CF₃, -CN, -NO₂,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ haloalkyl,
C₁₋₄ alkoxy, (C₁₋₄ haloalkyl)oxy,
C₃₋₁₀ cycloalkyl substituted with 0-2 R³³,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
10 aryl substituted with 0-5 R³³, and
5-6 membered heterocyclic ring system containing 1, 2,
or 3 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R³¹;

15

R¹², at each occurrence, is independently selected from

C₁₋₄ alkyl substituted with 0-1 R^{12a},
C₂₋₄ alkenyl substituted with 0-1 R^{12a},
C₂₋₄ alkynyl substituted with 0-1 R^{12a},
20 C₃₋₆ cycloalkyl substituted with 0-3 R³³,
phenyl substituted with 0-5 R³³;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
25 consisting of N, O, and S substituted with 0-3
R³¹;

R^{12a}, at each occurrence, is independently selected from
phenyl substituted with 0-5 R³³;

30 C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group

consisting of N, O, and S substituted with 0-3
R³¹;

5 R¹³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;

alternatively, R¹² and R¹³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R¹⁴)-;

10 alternatively, R¹² and R¹³ when attached to N may be
combined to form a 9- or 10-membered bicyclic
heterocyclic ring system containing from 1-3
heteroatoms selected from the group consisting of N,
O, and S; wherein said bicyclic heterocyclic ring
15 system is selected from indolyl, indolinyl, indazolyl,
benzimidazolyl, benzimidazolinyl, benztriazolyl,
benzoxazolyl, benzoxazolinyl, benzthiazolyl, and
dioxobenzthiazolyl; wherein said bicyclic heterocyclic
ring system is substituted with 0-1 R¹⁶;

20 R¹⁴, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;

25 R¹⁵, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;

R¹⁶, at each occurrence, is independently selected from
H, OH, F, Cl, CN, NO₂, methyl, ethyl, methoxy, ethoxy,
trifluoromethyl, and trifluoromethoxy;

30 R³¹, at each occurrence, is independently selected from
H, OH, halo, CF₃, methyl, ethyl, and propyl;

R³³, at each occurrence, is independently selected from

H, OH, halo, CN, NO₂, CF₃, SO₂R⁴⁵, NR⁴⁶R⁴⁷, -C(=O)H,
C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl,
C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkyl-oxy-,
C₁₋₄ alkyloxy-,
5 C₁₋₄ alkylthio-, C₁₋₄ alkyl-C(=O)-, C₁₋₄ alkyl-C(=O)NH-,
C₁₋₄ alkyl-OC(=O)-,
C₁₋₄ alkyl-C(=O)O-, C₃₋₆ cycloalkyl-oxy-, C₃₋₆
cycloalkylmethyl-oxy-;
C₁₋₆ alkyl substituted with OH, methoxy, ethoxy,
10 propoxy, or butoxy; and
C₂₋₆ alkenyl substituted with OH, methoxy, ethoxy,
propoxy, or butoxy;

R⁴¹, at each occurrence, is independently selected from
15 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,
C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl,
and C₁₋₃ alkyl;

R⁴², at each occurrence, is independently selected from
20 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN,
CH(=NH)NH₂, NHC(=NH)NH₂,
C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₃ alkoxy, C₁₋₃ haloalkyl,
C₃₋₆ cycloalkyl, and C₁₋₃ alkyl;

25 R⁴³ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
phenyl, or pyridyl, each substituted with 0-3 R⁴⁴;

R⁴⁴, at each occurrence, is independently selected from H,
halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂,
30 methyl, ethyl, propyl, butyl, methoxy, ethoxy,
propoxy, and butoxy;

R⁴⁵ is methyl, ethyl, propyl, or butyl;

R⁴⁶, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and butyl;

R⁴⁷, at each occurrence, is independently selected from
5 from H, methyl, ethyl, propyl, and butyl;

k is 1;

m is 1; and
10

n is 1 or 2.

6. A compound of Claim 2 wherein:

15 X is -NH-;

R¹ is selected from H,
C₁₋₅ alkyl substituted with 0-1 R²,
C₂₋₅ alkenyl substituted with 0-1 R², and
20 C₂₋₃ alkynyl substituted with 0-1 R²;

R² is C₃₋₆ cycloalkyl;

R⁵ is H, methyl, ethyl, or propyl;
25

R^{6a} is H, methyl, or ethyl;

R^{6b} is H;

30 R⁷ and R⁹, at each occurrence, are independently selected
from
H, F, Cl, -CH₃, -OCH₃, -CF₃, -OCF₃, -CN, and -NO₂,

R⁸ is selected from

methyl substituted with R^{11} ;
 ethenyl substituted with R^{11} ;
 OR^{12} , SR^{12} , $NR^{12}R^{13}$, $NR^{12}C(O)R^{15}$, $NR^{12}C(O)OR^{15}$,
 $NR^{12}S(O)_2R^{15}$, and $NR^{12}C(O)NHR^{15}$;

5

R^{11} is selected from

- phenyl- substituted with 0-5 fluoro;
- 2-($H_3CCH_2C(=O)$)-phenyl- substituted with R^{33} ;
- 2-($H_3CC(=O)$)-phenyl- substituted with R^{33} ;
- 10 2-($HC(=O)$)-phenyl- substituted with R^{33} ;
- 2-($H_3CCH(OH)$)-phenyl- substituted with R^{33} ;
- 2-($H_3CCH_2CH(OH)$)-phenyl- substituted with R^{33} ;
- 2-($HOCH_2$)-phenyl- substituted with R^{33} ;
- 2-($HOCH_2CH_2$)-phenyl- substituted with R^{33} ;
- 15 2-(H_3COCH_2)-phenyl- substituted with R^{33} ;
- 2-($H_3COCH_2CH_2$)-phenyl- substituted with R^{33} ;
- 2-($H_3CCH(OMe)$)-phenyl- substituted with R^{33} ;
- 2-($H_3COC(=O)$)-phenyl- substituted with R^{33} ;
- 2-($HOCH_2CH=CH$)-phenyl- substituted with R^{33} ;
- 20 2-(($MeOC(=O)CH=CH$))-phenyl- substituted with R^{33} ;
- 2-(methyl)-phenyl- substituted with R^{33} ;
- 2-(ethyl)-phenyl- substituted with R^{33} ;
- 2-(i-propyl)-phenyl- substituted with R^{33} ;
- 2-(F_3C)-phenyl- substituted with R^{33} ;
- 25 2-(NC)-phenyl- substituted with R^{33} ;
- 2-(H_3CO)-phenyl- substituted with R^{33} ;
- 2-(fluoro)-phenyl- substituted with R^{33} ;
- 2-(chloro)-phenyl- substituted with R^{33} ;
- 3-(NC)-phenyl- substituted with R^{33} ;
- 30 3-(H_3CO)-phenyl- substituted with R^{33} ;
- 3-(fluoro)-phenyl- substituted with R^{33} ;
- 3-(chloro)-phenyl- substituted with R^{33} ;

- 4-(NC)-phenyl- substituted with R^{33} ;
 4-(fluoro)-phenyl- substituted with R^{33} ;
 4-(chloro)-phenyl- substituted with R^{33} ;
 4-(H_3CS)-phenyl- substituted with R^{33} ;
 5 4-(H_3CO)-phenyl- substituted with R^{33} ;
 4-(ethoxy)-phenyl- substituted with R^{33} ;
 4-(i-propoxy)-phenyl- substituted with R^{33} ;
 4-(i-butoxy)-phenyl- substituted with R^{33} ;
 4-($H_3CCH_2CH_2C(=O)$)-phenyl- substituted with R^{33} ;
 10 4-($(H_3C)_2CHC(=O)$)-phenyl- substituted with R^{33} ;
 4-($H_3CCH_2C(=O)$)-phenyl- substituted with R^{33} ;
 4-($H_3CC(=O)$)-phenyl- substituted with R^{33} ;
 4-($H_3CCH_2CH_2CH(OH)$)-phenyl- substituted with R^{33} ;
 4-($(H_3C)_2CHCH(OH)$)-phenyl- substituted with R^{33} ;
 15 4-($H_3CCH_2CH(OH)$)-phenyl- substituted with R^{33} ;
 4-($H_3CCH(OH)$)-phenyl- substituted with R^{33} ;
 4-(cyclopropyloxy)-phenyl- substituted with R^{33} ;
 4-(cyclobutyloxy)-phenyl- substituted with R^{33} ; and
 4-(cyclopentyloxy)-phenyl- substituted with R^{33} ;

20

R^{12} is selected from

- phenyl- substituted with 0-5 fluoro;
 2-($H_3CCH_2C(=O)$)-phenyl- substituted with R^{33} ;
 2-($H_3CC(=O)$)-phenyl- substituted with R^{33} ;
 25 2-($HC(=O)$)-phenyl- substituted with R^{33} ;
 2-($H_3CCH(OH)$)-phenyl- substituted with R^{33} ;
 2-($H_3CCH_2CH(OH)$)-phenyl- substituted with R^{33} ;
 2-($HOCH_2$)-phenyl- substituted with R^{33} ;
 2-($HOCH_2CH_2$)-phenyl- substituted with R^{33} ;
 30 2-(H_3COCH_2)-phenyl- substituted with R^{33} ;
 2-($H_3COCH_2CH_2$)-phenyl- substituted with R^{33} ;
 2-($H_3CCH(OMe)$)-phenyl- substituted with R^{33} ;

- 2-(H₃COC(=O))-phenyl- substituted with R³³;
2-(HOCH₂CH=CH)-phenyl- substituted with R³³;
2-((MeOC=O)CH=CH)-phenyl- substituted with R³³;
2-(methyl)-phenyl- substituted with R³³;
5 2-(ethyl)-phenyl- substituted with R³³;
2-(i-propyl)-phenyl- substituted with R³³;
2-(F₃C)-phenyl- substituted with R³³;
2-(NC)-phenyl- substituted with R³³;
2-(H₃CO)-phenyl- substituted with R³³;
10 2-(fluoro)-phenyl- substituted with R³³;
2-(chloro)-phenyl- substituted with R³³;
3-(NC)-phenyl- substituted with R³³;
3-(H₃CO)-phenyl- substituted with R³³;
3-(fluoro)-phenyl- substituted with R³³;
15 3-(chloro)-phenyl- substituted with R³³;
4-(NC)-phenyl- substituted with R³³;
4-(fluoro)-phenyl- substituted with R³³;
4-(chloro)-phenyl- substituted with R³³;
4-(H₃CS)-phenyl- substituted with R³³;
20 4-(H₃CO)-phenyl- substituted with R³³;
4-(ethoxy)-phenyl- substituted with R³³;
4-(i-propoxy)-phenyl- substituted with R³³;
4-(i-butoxy)-phenyl- substituted with R³³;
4-(H₃CCH₂CH₂C(=O))-phenyl- substituted with R³³;
25 4-((H₃C)₂CHC(=O))-phenyl- substituted with R³³;
4-(H₃CCH₂C(=O))-phenyl- substituted with R³³;
4-(H₃CC(=O))-phenyl- substituted with R³³;
4-(H₃CCH₂CH₂CH(OH))-phenyl- substituted with R³³;
4-((H₃C)₂CHCH(OH))-phenyl- substituted with R³³;
30 4-(H₃CCH₂CH(OH))-phenyl- substituted with R³³;
4-(H₃CCH(OH))-phenyl- substituted with R³³;
4-(cyclopropyloxy)-phenyl- substituted with R³³;

4-(cyclobutyloxy)-phenyl- substituted with R^{33} ; and
4-(cyclopentyloxy)-phenyl- substituted with R^{33} ;

R^{13} is H, methyl, or ethyl;

5

alternatively, R^{12} and R^{13} join to form a 5- or 6-membered ring selected from pyrrolyl, pyrrolidinyl, imidazolyl, piperidinyl, piperiziny, methylpiperiziny, and morpholinyl;

10

alternatively, R^{12} and R^{13} when attached to N may be combined to form a 9- or 10-membered bicyclic heterocyclic ring system containing from 1-3 heteroatoms selected from the group consisting of N, O, and S; wherein said bicyclic heterocyclic ring system is selected from indolyl, indolinyl, indazolyl, benzimidazolyl, benzimidazolinyl, benztriazolyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, and dioxobenzthiazolyl; wherein said bicyclic heterocyclic ring system is substituted with 0-1 R^{16} ;

15

20

R^{15} is H, methyl, ethyl, propyl, or butyl;

25 R^{16} , at each occurrence, is independently selected from H, OH, F, Cl, CN, NO_2 , methyl, ethyl, methoxy, ethoxy, trifluoromethyl, and trifluoromethoxy;

R^{33} , at each occurrence, is independently selected from
30 H, F, Cl, $-\text{CH}_3$, $-\text{OCH}_3$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{CN}$, and $-\text{NO}_2$;

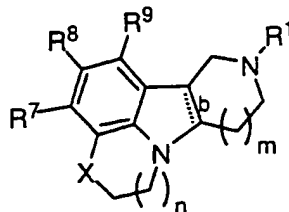
k is 1;

m is 1; and

n is 1 or 2.

35

7. A compound of Claim 2 of Formula (I-a)



(I-a)

wherein:

b is a single bond or a double bond;

X is -NR^{10A}-;

R¹ is selected from

hydrogen, methyl, ethyl, n-propyl, n-butyl, s-butyl,
t-butyl, n-pentyl, n-hexyl, 2-propyl, 2-butyl, 2-pentyl,
2-hexyl, 2-methylpropyl, 2-methylbutyl, 2-methylpentyl,
2-ethylbutyl, 3-methylpentyl, 3-methylbutyl,
4-methylpentyl, 2-fluoroethyl, 2,2-difluoroethyl,
2,2,2-trifluoroethyl,

2-propenyl, 2-methyl-2-propenyl, trans-2-butenyl,
3-methyl-butenyl, 3-butenyl, trans-2-pentenyl,
cis-2-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl,
3,3-dichloro-2-propenyl, trans-3-phenyl-2-propenyl,

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl,
cyclohexylmethyl,

benzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl,
2,5-dimethylbenzyl, 2,4-dimethylbenzyl, 3,5-
dimethylbenzyl,
2,4,6-trimethyl-benzyl, 3-methoxy-benzyl, 3,5-dimethoxy-
5 benzyl, pentafluorobenzyl, 2-phenylethyl, 1-phenyl-2-
propyl, 4-phenylbutyl, 4-phenylbenzyl, 2-phenylbenzyl,

(2,3-dimethoxy-phenyl)C(=O)-, (2,5-dimethoxy-
phenyl)C(=O)-, (3,4-dimethoxy-phenyl)C(=O)-,
10 (3,5-dimethoxy-phenyl)C(=O)-, cyclopropyl-C(=O)-,
isopropyl-C(=O)-, ethyl-CO₂-, propyl-CO₂-, t-butyl-CO₂-,
2,6-dimethoxy-benzyl, 2,4-dimethoxy-benzyl,
2,4,6-trimethoxy-benzyl, 2,3-dimethoxy-benzyl,
2,4,5-trimethoxy-benzyl, 2,3,4-trimethoxy-benzyl,
15 3,4-dimethoxy-benzyl, 3,4,5-trimethoxy-benzyl,
(4-fluoro-phenyl)ethyl,

-CH=CH₂, -CH₂-CH=CH₂, -CH=CH-CH₃, -C≡CH, -C≡C-CH₃, and
-CH₂-C≡CH;

20

R⁷, R⁸, and R⁹, at each occurrence, are independently
selected from

hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl,
propyl, isopropyl, butyl, t-butyl, nitro,
25 trifluoromethyl, methoxy, ethoxy, isopropoxy,
trifluoromethoxy, phenyl,

30

methylC(=O)-, ethylC(=O)-, propylC(=O)-, isopropylC(=O)-,
butylC(=O)-, phenylC(=O)-,

methylCO₂-, ethylCO₂-, propylCO₂-, isopropylCO₂-,
butylCO₂-, phenylCO₂-,

dimethylamino-S(=O)-, diethylamino-S(=O)-,

- dipropylamino-S(=O)-, di-isopropylamino-S(=O)-,
dibutylamino-S(=O)-, diphenylamino-S(=O)-,
- 5 dimethylamino-SO₂-, diethylamino-SO₂-, dipropylamino-SO₂-, di-isopropylamino-SO₂-, dibutylamino-SO₂-,
diphenylamino-SO₂-,
- 10 dimethylamino-C(=O)-, diethylamino-C(=O)-,
dipropylamino-C(=O)-, di-isopropylamino-C(=O)-,
dibutylamino-C(=O)-, diphenylamino-C(=O)-,
- 15 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-cyanophenyl, 2-methylphenyl, 2-trifluoromethylphenyl,
2-methoxyphenyl, 2-trifluoromethoxyphenyl,
- 3-chlorophenyl, 3-fluorophenyl, 3-bromophenyl,
3-cyanophenyl, 3-methylphenyl, 3-ethylphenyl,
3-propylphenyl, 3-isopropylphenyl, 3-butylphenyl,
3-trifluoromethylphenyl, 3-methoxyphenyl,
- 20 3-isopropoxyphenyl, 3-trifluoromethoxyphenyl,
3-thiomethoxyphenyl,
- 4-chlorophenyl, 4-fluorophenyl, 4-bromophenyl,
4-cyanophenyl, 4-methylphenyl, 4-ethylphenyl,
- 25 4-propylphenyl, 4-isopropylphenyl, 4-butylphenyl,
4-trifluoromethylphenyl, 4-methoxyphenyl,
4-isopropoxyphenyl, 4-trifluoromethoxyphenyl,
4-thiomethoxyphenyl,
- 30 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,3-dimethylphenyl,
2,3-ditrifluoromethylphenyl, 2,3-dimethoxyphenyl,
2,3-ditrifluoromethoxyphenyl,

- 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,4-dimethylphenyl,
2,4-ditrifluoromethylphenyl, 2,4-dimethoxyphenyl,
2,4-ditrifluoromethoxyphenyl,
- 5 2,5-dichlorophenyl, 2,5-difluorophenyl, 2,5-dimethylphenyl,
2,5-ditrifluoromethylphenyl, 2,5-dimethoxyphenyl,
2,5-ditrifluoromethoxyphenyl,
- 10 2,6-dichlorophenyl, 2,6-difluorophenyl, 2,6-dimethylphenyl,
2,6-ditrifluoromethylphenyl, 2,6-dimethoxyphenyl,
2,6-ditrifluoromethoxyphenyl,
- 15 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-dimethylphenyl,
3,4-ditrifluoromethylphenyl, 3,4-dimethoxyphenyl,
3,4-ditrifluoromethoxyphenyl,
- 20 2,4,6-trichlorophenyl, 2,4,6-trifluorophenyl,
2,4,6-trimethylphenyl, 2,4,6-tritrifluoromethylphenyl,
2,4,6-trimethoxyphenyl, 2,4,6-tritrifluoromethoxyphenyl,
- 25 2-chloro-4-CF₃-phenyl, 2-fluoro-3-chloro-phenyl,
2-chloro-4-CF₃-phenyl, 2-chloro-4-methoxy-phenyl,
2-methoxy-4-isopropyl-phenyl, 2-CF₃-4-methoxy-phenyl,
2-methyl-4-methoxy-5-fluoro-phenyl,
2-methyl-4-methoxy-phenyl, 2-chloro-4-CF₃O-phenyl,
- 30 2,4,5-trimethyl-phenyl, 2-methyl-4-chloro-phenyl,
- methyl-C(=O)NH-, ethyl-C(=O)NH-, propyl-C(=O)NH-,
isopropyl-C(=O)NH-, butyl-C(=O)NH-, phenyl-C(=O)NH-,
- 35 4-acetylphenyl, 3-acetamidophenyl, 4-pyridyl, 2-furanyl,

- 2-thiophenyl, 2-naphthyl;
- 2-Me-5-F-phenyl, 2-F-5-Me-phenyl, 2-MeO-5-F-phenyl,
 2-Me-3-Cl-phenyl, 3-NO₂-phenyl, 2-NO₂-phenyl,
 5 2-Cl-3-Me-phenyl, 2-Me-4-EtO-phenyl, 2-Me-4-F-phenyl,
 2-Cl-6-F-phenyl, 2-Cl-4-(CHF₂)O-phenyl,
 2,4-diMeO-6-F-phenyl, 2-CF₃-6-F-phenyl,
 2-MeS-phenyl, 2,6-diCl-4-MeO-phenyl,
 2,3,4-triF-phenyl, 2,6-diF-4-Cl-phenyl,
 10 2,3,4,6-tetraF-phenyl, 2,3,4,5,6-pentaF-phenyl,
 2-CF₃-4-EtO-phenyl, 2-CF₃-4-iPrO-phenyl,
 2-CF₃-4-Cl-phenyl, 2-CF₃-4-F-phenyl, 2-Cl-4-EtO-phenyl,
 2-Cl-4-iPrO-phenyl, 2-Et-4-MeO-phenyl,
 2-CHO-4-MeO-phenyl, 2-CH(OH)Me-4-MeO-phenyl,
 15 2-CH(OMe)Me-4-MeO-phenyl, 2-C(=O)Me-4-MeO-phenyl,
 2-CH₂(OH)-4-MeO-phenyl, 2-CH₂(OMe)-4-MeO-phenyl,
 2-CH(OH)Et-4-MeO-phenyl, 2-C(=O)Et-4-MeO-phenyl,
 (Z)-2-CH=CHCO₂Me-4-MeO-phenyl,
 2-CH₂CH₂CO₂Me-4-MeO-phenyl,
 20 (Z)-2-CH=CHCH₂(OH)-4-MeO-phenyl,
 (E)-2-CH=CHCO₂Me-4-MeO-phenyl,
 (E)-2-CH=CHCH₂(OH)-4-MeO-phenyl,
 2-CH₂CH₂OMe-4-MeO-phenyl,
 2-F-4-MeO-phenyl, 2-Cl-4-F-phenyl,
 25 (2-Cl-phenyl)-CH=CH-, (3-Cl-phenyl)-CH=CH-,
 (2,6-diF-phenyl)-CH=CH-, -CH₂CH=CH₂,
 phenyl-CH=CH-, (2-Me-4-MeO-phenyl)-CH=CH-,
 cyclohexyl, cyclopentyl, cyclohexylmethyl,
 -CH₂CH₂CO₂Et, -(CH₂)₃CO₂Et, -(CH₂)₄CO₂Et,
 30 benzyl, 2-F-benzyl, 3-F-benzyl, 4-F-benzyl,
 3-MeO-benzyl, 3-OH-benzyl, 2-MeO-benzyl,
 2-OH-benzyl, 2-CO₂Me-3-MeO-phenyl,
 2-Me-4-CN-phenyl, 2-Me-3-CN-phenyl, 2-CF₃-4-CN-phenyl,
 3-CHO-phenyl, 3-CH₂(OH)-phenyl, 3-CH₂(OMe)-phenyl,

3-CH₂(NMe₂)-phenyl, 3-CN-4-F-phenyl,
 3-CONH₂-4-F-phenyl, 2-CH₂(NH₂)-4-MeO-phenyl-,
 phenyl-NH-, (4-F-phenyl)-NH-, (2,4-diCl-phenyl)-NH-,
 phenyl-C(=O)NH-, benzyl-NH-, (2-Me-4-MeO-phenyl)-NH-,
 5 (2-F-4-MeO-phenyl)-NH-, (2-Me-4-F-phenyl)-NH-,
 phenyl-S-, -NMe₂, 1-pyrrolidinyl, and
 -N(tosylate)₂,

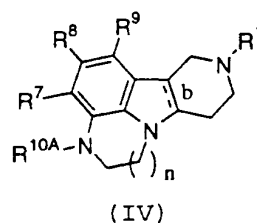
provided that two of R⁷, R⁸, and R⁹, are independently
 10 selected from hydrogen, fluoro, chloro, bromo, cyano,
 methyl, ethyl, propyl, isopropyl, butyl, t-butyl, nitro,
 trifluoromethyl, methoxy, ethoxy, isopropoxy, and
 trifluoromethoxy;

15 R^{10A} is selected from hydrogen, methyl, ethyl, benzyl and 4-
 fluorobenzyl;

m is 1; and

20 n is 1 or 2.

8. A compound of Claim 7 of Formula (IV)



25

wherein:

b is a single bond, wherein the bridge hydrogens are in a
 30 cis position;

R¹ is selected from

hydrogen, methyl, ethyl, n-propyl, n-butyl, s-butyl,
t-butyl, n-pentyl, n-hexyl, 2-propyl, 2-butyl, 2-pentyl,
2-hexyl, 2-methylpropyl, 2-methylbutyl, 2-methylpentyl,
5 2-ethylbutyl, 3-methylpentyl, 3-methylbutyl,
4-methylpentyl, 2-fluoroethyl, 2,2-difluoroethyl,
2,2,2-trifluoroethyl, 2-propenyl, 2-methyl-2-propenyl,
trans-2-butenyl, 3-methyl-butenyl, 3-butenyl,
trans-2-pentenyl, cis-2-pentenyl, 4-pentenyl,
10 4-methyl-3-pentenyl, 3,3-dichloro-2-propenyl,
trans-3-phenyl-2-propenyl, cyclopropyl, cyclobutyl,
cyclopentyl, cyclohexyl, cyclopropylmethyl,
cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl,
-CH=CH₂, -CH₂-CH=CH₂, -CH=CH-CH₃, -C≡CH, -C≡C-CH₃,
15 and -CH₂-C≡CH;

R⁷ and R⁹, at each occurrence, are independently selected
from hydrogen, fluoro, methyl, trifluoromethyl, and
methoxy;

20

R⁸ is selected from

hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl,
propyl, isopropyl, butyl, t-butyl, nitro,
trifluoromethyl, methoxy, ethoxy, isopropoxy,
25 trifluoromethoxy, phenyl,

methylC(=O)-, ethylC(=O)-, propylC(=O)-, isopropylC(=O)-,
butylC(=O)-, phenylC(=O)-,

30 methylCO₂-, ethylCO₂-, propylCO₂-, isopropylCO₂-,
butylCO₂-, phenylCO₂-,

dimethylamino-S(=O)-, diethylamino-S(=O)-,
dipropylamino-S(=O)-, di-isopropylamino-S(=O)-,
35 dibutylamino-S(=O)-, diphenylamino-S(=O)-,

- dimethylamino-SO₂-, diethylamino-SO₂-, dipropylamino-SO₂-, di-isopropylamino-SO₂-, dibutylamino-SO₂-, diphenylamino-SO₂-,
- 5 dimethylamino-C(=O)-, diethylamino-C(=O)-, dipropylamino-C(=O)-, di-isopropylamino-C(=O)-, dibutylamino-C(=O)-, diphenylamino-C(=O)-,
- 10 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-cyanophenyl, 2-methylphenyl, 2-trifluoromethylphenyl, 2-methoxyphenyl, 2-trifluoromethoxyphenyl,
- 15 3-chlorophenyl, 3-fluorophenyl, 3-bromophenyl, 3-cyanophenyl, 3-methylphenyl, 3-ethylphenyl, 3-propylphenyl, 3-isopropylphenyl, 3-butylphenyl, 3-trifluoromethylphenyl, 3-methoxyphenyl, 3-isopropoxyphenyl, 3-trifluoromethoxyphenyl, 3-thiomethoxyphenyl,
- 20 4-chlorophenyl, 4-fluorophenyl, 4-bromophenyl, 4-cyanophenyl, 4-methylphenyl, 4-ethylphenyl, 4-propylphenyl, 4-isopropylphenyl, 4-butylphenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 4-isopropoxyphenyl, 4-trifluoromethoxyphenyl, 4-thiomethoxyphenyl,
- 25 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,3-dimethylphenyl, 2,3-ditrifluoromethylphenyl, 2,3-dimethoxyphenyl, 2,3-ditrifluoromethoxyphenyl,
- 30 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,4-dimethylphenyl, 2,4-ditrifluoromethylphenyl, 2,4-dimethoxyphenyl,
- 35

- 2,4-ditrifluoromethoxyphenyl,
- 2,5-dichlorophenyl, 2,5-difluorophenyl, 2,5-dimethylphenyl,
- 5 2,5-ditrifluoromethylphenyl, 2,5-dimethoxyphenyl,
2,5-ditrifluoromethoxyphenyl,
- 2,6-dichlorophenyl, 2,6-difluorophenyl, 2,6-dimethylphenyl,
- 10 2,6-ditrifluoromethylphenyl, 2,6-dimethoxyphenyl,
2,6-ditrifluoromethoxyphenyl,
- 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-dimethylphenyl,
- 15 3,4-ditrifluoromethylphenyl, 3,4-dimethoxyphenyl,
3,4-ditrifluoromethoxyphenyl,
- 2,4,6-trichlorophenyl, 2,4,6-trifluorophenyl,
2,4,6-trimethylphenyl, 2,4,6-tritrifluoromethylphenyl,
- 20 2,4,6-trimethoxyphenyl, 2,4,6-tritrifluoromethoxyphenyl,
- 2-chloro-4-CF₃-phenyl, 2-fluoro-3-chloro-phenyl,
2-chloro-4-CF₃-phenyl, 2-chloro-4-methoxy-phenyl,
2-methoxy-4-isopropyl-phenyl, 2-CF₃-4-methoxy-phenyl,
- 25 2-methyl-4-methoxy-5-fluoro-phenyl,
2-methyl-4-methoxy-phenyl, 2-chloro-4-CF₃O-phenyl,
2,4,5-trimethyl-phenyl, 2-methyl-4-chloro-phenyl,
- methyl-C(=O)NH-, ethyl-C(=O)NH-, propyl-C(=O)NH-,
30 isopropyl-C(=O)NH-, butyl-C(=O)NH-, phenyl-C(=O)NH-,
- 4-acetylphenyl, 3-acetamidophenyl, 4-pyridyl, 2-furanyl,
2-thiophenyl, 2-naphthyl;
- 35 2-Me-5-F-phenyl, 2-F-5-Me-phenyl, 2-MeO-5-F-phenyl,

- 2-Me-3-Cl-phenyl, 3-NO₂-phenyl, 2-NO₂-phenyl,
 2-Cl-3-Me-phenyl, 2-Me-4-EtO-phenyl, 2-Me-4-F-phenyl,
 2-Cl-6-F-phenyl, 2-Cl-4-(CHF₂)O-phenyl,
 2,4-diMeO-6-F-phenyl, 2-CF₃-6-F-phenyl,
 5 2-MeS-phenyl, 2,6-diCl-4-MeO-phenyl,
 2,3,4-triF-phenyl, 2,6-diF-4-Cl-phenyl,
 2,3,4,6-tetraF-phenyl, 2,3,4,5,6-pentaF-phenyl,
 2-CF₃-4-EtO-phenyl, 2-CF₃-4-iPrO-phenyl,
 2-CF₃-4-Cl-phenyl, 2-CF₃-4-F-phenyl, 2-Cl-4-EtO-phenyl,
 10 2-Cl-4-iPrO-phenyl, 2-Et-4-MeO-phenyl,
 2-CHO-4-MeO-phenyl, 2-CH(OH)Me-4-MeO-phenyl,
 2-CH(OMe)Me-4-MeO-phenyl, 2-C(=O)Me-4-MeO-phenyl,
 2-CH₂(OH)-4-MeO-phenyl, 2-CH₂(OMe)-4-MeO-phenyl,
 2-CH(OH)Et-4-MeO-phenyl, 2-C(=O)Et-4-MeO-phenyl,
 15 (Z)-2-CH=CHCO₂Me-4-MeO-phenyl,
 2-CH₂CH₂CO₂Me-4-MeO-phenyl,
 (Z)-2-CH=CHCH₂(OH)-4-MeO-phenyl,
 (E)-2-CH=CHCO₂Me-4-MeO-phenyl,
 (E)-2-CH=CHCH₂(OH)-4-MeO-phenyl,
 20 2-CH₂CH₂OMe-4-MeO-phenyl,
 2-F-4-MeO-phenyl, 2-Cl-4-F-phenyl,
 (2-Cl-phenyl)-CH=CH-, (3-Cl-phenyl)-CH=CH-,
 (2,6-diF-phenyl)-CH=CH-, -CH₂CH=CH₂,
 phenyl-CH=CH-, (2-Me-4-MeO-phenyl)-CH=CH-,
 25 cyclohexyl, cyclopentyl, cyclohexylmethyl,
 -CH₂CH₂CO₂Et, -(CH₂)₃CO₂Et, -(CH₂)₄CO₂Et,
 benzyl, 2-F-benzyl, 3-F-benzyl, 4-F-benzyl,
 3-MeO-benzyl, 3-OH-benzyl, 2-MeO-benzyl,
 2-OH-benzyl, 2-CO₂Me-3-MeO-phenyl,
 30 2-Me-4-CN-phenyl, 2-Me-3-CN-phenyl, 2-CF₃-4-CN-phenyl,
 3-CHO-phenyl, 3-CH₂(OH)-phenyl, 3-CH₂(OMe)-phenyl,
 3-CH₂(NMe₂)-phenyl, 3-CN-4-F-phenyl,
 3-CONH₂-4-F-phenyl, 2-CH₂(NH₂)-4-MeO-phenyl-,
 phenyl-NH-, (4-F-phenyl)-NH-, (2,4-diCl-phenyl)-NH-,

phenyl-C(=O)NH-, benzyl-NH-, (2-Me-4-MeO-phenyl)-NH-,
(2-F-4-MeO-phenyl)-NH-, (2-Me-4-F-phenyl)-NH-,
phenyl-S-, -NMe₂, 1-pyrrolidinyl, and
-N(tosylate)₂;

5

R^{10A} is selected from hydrogen, methyl, ethyl, 4-fluorobenzyl and benzyl; and

n is 1 or 2.

10

9. A compound of Claim 1 wherein:

X is -NR^{10A}-, -C(=O)NR^{10A}-, or -NR^{10A}C(=O)-;

15

R¹ is selected from

C₁₋₆ alkyl substituted with Z,

C₂₋₆ alkenyl substituted with Z,

C₂₋₆ alkynyl substituted with Z,

20

C₃₋₆ cycloalkyl substituted with Z,

aryl substituted with Z,

5-6 membered heterocyclic ring system containing at

least one heteroatom selected from the group

consisting of N, O, and S, said heterocyclic ring

25

system substituted with Z;

C₁₋₆ alkyl substituted with 0-2 R²,

C₂₋₆ alkenyl substituted with 0-2 R²,

C₂₋₆ alkynyl substituted with 0-2 R²,

aryl substituted with 0-2 R², and

30

5-6 membered heterocyclic ring system containing at

least one heteroatom selected from the group

consisting of N, O, and S, said heterocyclic ring

system substituted with 0-2 R²;

Z is selected from H,

- CH(OH)R²,
- C(ethylenedioxy)R²,
- OR²,
- 5 -SR²,
- NR²R³,
- C(O)R²,
- C(O)NR²R³,
- NR³C(O)R²,
- 10 -C(O)OR²,
- OC(O)R²,
- CH(=NR⁴)NR²R³,
- NHC(=NR⁴)NR²R³,
- S(O)R²,
- 15 -S(O)₂R²,
- S(O)₂NR²R³, and -NR³S(O)₂R²;

R², at each occurrence, is independently selected from

- C₁₋₄ alkyl,
- 20 C₂₋₄ alkenyl,
- C₂₋₄ alkynyl,
- C₃₋₆ cycloalkyl,
- aryl substituted with 0-5 R⁴²;
- C₃₋₁₀ carbocyclic residue substituted with 0-3 R⁴¹, and
- 25 5-10 membered heterocyclic ring system containing from
- 1-4 heteroatoms selected from the group
- consisting of N, O, and S substituted with 0-3
- R⁴¹;

30 R³, at each occurrence, is independently selected from

- H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, and
- C₁₋₄ alkoxy;

alternatively, R² and R³ join to form a 5- or 6-membered ring optionally substituted with -O- or -N(R⁴)-;

5 R⁴, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and butyl;

R⁵ is H, methyl, ethyl, propyl, or butyl;

10 R^{6a} is selected from
H, -OH, -NR⁴⁶R⁴⁷, -CF₃,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₃₋₆ cycloalkyl, and
aryl substituted with 0-3 R⁴⁴;

15 R^{6b} is H;

R⁷, R⁸, and R⁹, at each occurrence, are independently selected from
H, halo, -CF₃, -OCF₃, -OH, -CN, -NO₂, -NR⁴⁶R⁴⁷,
20 C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ haloalkyl, C₁₋₈ alkoxy, (C₁₋₄ haloalkyl)oxy,
C₁₋₄ alkyl substituted with 0-2 R¹¹,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³,
25 5-10 membered heterocyclic ring system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-3 R³¹;

30 OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², OC(O)OR¹²,
CH(=NR¹⁴)NR¹²R¹³, NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹²,
S(O)NR¹²R¹³, S(O)₂NR¹²R¹³, NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹²,

$\text{NR}^{12}\text{C}(\text{O})\text{R}^{15}$, $\text{NR}^{12}\text{C}(\text{O})\text{OR}^{15}$, $\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{15}$, and
 $\text{NR}^{12}\text{C}(\text{O})\text{NHR}^{15}$;

$\text{R}^{10\text{A}}$ is selected from H,

- 5 C_{1-6} alkyl substituted with 0-1 $\text{R}^{10\text{B}}$,
 C_{2-6} alkenyl substituted with 0-1 $\text{R}^{10\text{B}}$,
 C_{2-6} alkynyl substituted with 0-1 $\text{R}^{10\text{B}}$, and
 C_{1-6} alkoxy;

10 $\text{R}^{10\text{B}}$ is selected from

C_{1-4} alkoxy,
 C_{3-6} cycloalkyl,

C_{3-10} carbocyclic residue substituted with 0-3 R^{33} ,
 phenyl substituted with 0-3 R^{33} , and

- 15 5-6 membered heterocyclic ring system containing 1, 2,
 or 3 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-2
 R^{44} ;

20 R^{11} is selected from

 H, halo, $-\text{CF}_3$, $-\text{CN}$, $-\text{NO}_2$,

C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-4} haloalkyl,
 C_{1-8} alkoxy, C_{3-10} cycloalkyl,

C_{3-10} carbocyclic residue substituted with 0-3 R^{33} ,

- 25 aryl substituted with 0-5 R^{33} ,

 5-10 membered heterocyclic ring system containing from
 1-4 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-3
 R^{31} ;

30

OR^{12} , SR^{12} , $\text{NR}^{12}\text{R}^{13}$, $\text{C}(\text{O})\text{H}$, $\text{C}(\text{O})\text{R}^{12}$, $\text{C}(\text{O})\text{NR}^{12}\text{R}^{13}$,
 $\text{NR}^{14}\text{C}(\text{O})\text{R}^{12}$, $\text{C}(\text{O})\text{OR}^{12}$, $\text{OC}(\text{O})\text{R}^{12}$, $\text{OC}(\text{O})\text{OR}^{12}$,
 $\text{CH}(=\text{NR}^{14})\text{NR}^{12}\text{R}^{13}$, $\text{NHC}(=\text{NR}^{14})\text{NR}^{12}\text{R}^{13}$, $\text{S}(\text{O})\text{R}^{12}$,

$S(O)_2R^{12}$, $S(O)NR^{12}R^{13}$, $S(O)_2NR^{12}R^{13}$, $NR^{14}S(O)R^{12}$,
and $NR^{14}S(O)_2R^{12}$;

R^{12} , at each occurrence, is independently selected from
5 C_{1-4} alkyl,
 C_{2-4} alkenyl,
 C_{2-4} alkynyl,
 C_{3-6} cycloalkyl,
phenyl substituted with 0-5 R^{33} ;
10 C_{3-10} carbocyclic residue substituted with 0-3 R^{33} , and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
 R^{31} ;

15

R^{13} , at each occurrence, is independently selected from
H, C_{1-4} alkyl, C_{2-4} alkenyl, and C_{2-4} alkynyl;

alternatively, R^{12} and R^{13} join to form a 5- or 6-membered
20 ring optionally substituted with -O- or -N(R^{14})-;

R^{14} , at each occurrence, is independently selected from H
and C_{1-4} alkyl;

25 R^{31} , at each occurrence, is independently selected from
H, OH, halo, CF_3 , SO_2R^{45} , $NR^{46}R^{47}$, methyl, ethyl, and
propyl;

R^{33} , at each occurrence, is independently selected from
30 H, OH, halo, CN, NO_2 , CF_3 , SO_2R^{45} , $NR^{46}R^{47}$,
 C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{3-5} cycloalkyl,
 C_{1-3} haloalkyl, C_{1-3} haloalkyl-oxy-, C_{1-3} alkyloxy-,
, C_{1-3} alkylthio-, C_{1-3} alkyl-C(=O)-, and C_{1-3}
alkyl-C(=O)NH-;

R⁴¹, at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, =O,
C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl
5 C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴², and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
10 R⁴⁴;

R⁴², at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, SR⁴⁵, NR⁴⁶R⁴⁷, OR⁴⁸,
NO₂, CN, CH(=NH)NH₂, NHC(=NH)NH₂,
15 C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
C₃₋₆ cycloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴⁴, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
20 consisting of N, O, and S substituted with 0-3
R⁴⁴;

R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;
25

R⁴⁴, at each occurrence, is independently selected from H,
halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂,
C₁₋₄ alkyl, and C₁₋₄ alkoxy;

30 R⁴⁵ is C₁₋₄ alkyl;

R⁴⁶, at each occurrence, is independently selected from H
and C₁₋₄ alkyl;

R⁴⁷, at each occurrence, is independently selected from H,
C₁₋₄ alkyl, -C(=O)NH(C₁₋₄ alkyl), -SO₂(C₁₋₄ alkyl),
-SO₂(phenyl), -C(=O)O(C₁₋₄ alkyl), -C(=O)(C₁₋₄ alkyl),
5 and -C(=O)H;

R⁴⁸, at each occurrence, is independently selected from H,
C₁₋₄ alkyl, -C(=O)NH(C₁₋₄ alkyl), -C(=O)O(C₁₋₄ alkyl),
-C(=O)(C₁₋₄ alkyl), and -C(=O)H;

10

k is 1 or 2;

m is 0, 1, or 2; and

15

n is 1 or 2.

10. A compound of Claim 9 wherein:

X is -NR^{10A}-;

20

R¹ is selected from

C₂₋₅ alkyl substituted with Z,
C₂₋₅ alkenyl substituted with Z,
C₂₋₅ alkynyl substituted with Z,
25 C₃₋₆ cycloalkyl substituted with Z,
aryl substituted with Z,
5-6 membered heterocyclic ring system containing at
least one heteroatom selected from the group
consisting of N, O, and S, said heterocyclic ring
30 system substituted with Z;
C₁₋₅ alkyl substituted with 0-2 R²,
C₂₋₅ alkenyl substituted with 0-2 R², and
C₂₋₅ alkynyl substituted with 0-2 R²;

Z is selected from H,

- CH(OH)R²,
- C(ethylenedioxy)R²,
- OR²,
- 5 -SR²,
- NR²R³,
- C(O)R²,
- C(O)NR²R³,
- NR³C(O)R²,
- 10 -C(O)OR²,
- OC(O)R²,
- CH(=NR⁴)NR²R³,
- NHC(=NR⁴)NR²R³,
- S(O)R²,
- 15 -S(O)₂R²,
- S(O)₂NR²R³, and -NR³S(O)₂R²;

R², at each occurrence, is independently selected from

- C₁₋₄ alkyl,
- 20 C₂₋₄ alkenyl,
- C₂₋₄ alkynyl,
- C₃₋₆ cycloalkyl,
- aryl substituted with 0-5 R⁴²;
- C₃₋₁₀ carbocyclic residue substituted with 0-3 R⁴¹, and
- 25 5-10 membered heterocyclic ring system containing from
- 1-4 heteroatoms selected from the group
- consisting of N, O, and S substituted with 0-3
- R⁴¹;

30 R³, at each occurrence, is independently selected from

- H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, and
- C₁₋₄ alkoxy;

alternatively, R² and R³ join to form a 5- or 6-membered ring optionally substituted with -O- or -N(R⁴)-;

5 R⁴, at each occurrence, is independently selected from H, methyl, ethyl, propyl, and butyl;

R⁵ is H, methyl, or ethyl;

R^{6a} is selected from
10 H, -OH, -NR⁴⁶R⁴⁷, -CF₃,
C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, and C₃₋₆ cycloalkyl;

R^{6b} is H;
15

R⁷, R⁸, and R⁹, at each occurrence, are independently selected from
H, halo, -CF₃, -OCF₃, -OH, -OCH₃, -CN, -NO₂, -NR⁴⁶R⁴⁷,
C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl,
20 C₁₋₆ alkoxy, (C₁₋₄ haloalkyl)oxy,
C₁₋₄ alkyl substituted with 0-2 R¹¹,
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
aryl substituted with 0-5 R³³,
5-10 membered heterocyclic ring system containing from
25 1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3 R³¹;

OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
30 NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², CH(=NR¹⁴)NR¹²R¹³,
NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)₂NR¹²R¹³,
NR¹⁴S(O)₂R¹², NR¹⁴S(O)R¹², NR¹⁴S(O)₂R¹², NR¹²C(O)R¹⁵,
NR¹²C(O)OR¹⁵, NR¹²S(O)₂R¹⁵, and NR¹²C(O)NHR¹⁵;

R^{10A} is selected from H,

- C₁₋₆ alkyl substituted with 0-1 R^{10B},
- C₂₋₆ alkenyl substituted with 0-1 R^{10B},
- 5 C₂₋₆ alkynyl substituted with 0-1 R^{10B}, and
- C₁₋₆ alkoxy;

R^{10B} is selected from

- C₁₋₄ alkoxy,
- 10 C₃₋₆ cycloalkyl,
- C₃₋₆ carbocyclic residue substituted with 0-3 R³³,
- phenyl substituted with 0-3 R³³, and
- 5-6 membered heterocyclic ring system containing 1, 2,
- or 3 heteroatoms selected from the group
- 15 consisting of N, O, and S substituted with 0-2
- R⁴⁴;

R¹¹ is selected from

- H, halo, -CF₃, -OCF₃, -OH, -OCH₃, -CN, -NO₂, -NR⁴⁶R⁴⁷,
- 20 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ haloalkyl,
- C₁₋₆ alkoxy, (C₁₋₄ haloalkyl)oxy,
- C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³,
- aryl substituted with 0-5 R³³,
- 5-10 membered heterocyclic ring system containing from
- 25 1-4 heteroatoms selected from the group
- consisting of N, O, and S substituted with 0-3
- R³¹;

- OR¹², SR¹², NR¹²R¹³, C(O)H, C(O)R¹², C(O)NR¹²R¹³,
- 30 NR¹⁴C(O)R¹², C(O)OR¹², OC(O)R¹², CH(=NR¹⁴)NR¹²R¹³,
- NHC(=NR¹⁴)NR¹²R¹³, S(O)R¹², S(O)₂R¹², S(O)₂NR¹²R¹³,
- and NR¹⁴S(O)₂R¹²;

R¹², at each occurrence, is independently selected from
C₁₋₄ alkyl,
C₂₋₄ alkenyl,
C₂₋₄ alkynyl,
5 C₃₋₆ cycloalkyl,
phenyl substituted with 0-5 R³³;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R³³, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
10 consisting of N, O, and S substituted with 0-3
R³¹;

R¹³, at each occurrence, is independently selected from
H, C₁₋₄ alkyl, C₂₋₄ alkenyl, and C₂₋₄ alkynyl;
15
alternatively, R¹² and R¹³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R¹⁴)-;

R¹⁴, at each occurrence, is independently selected from H
20 and C₁₋₄ alkyl;

R³¹, at each occurrence, is independently selected from
H, OH, halo, CF₃, methyl, and ethyl;

25 R³³, at each occurrence, is independently selected from
H, OH, halo, CN, NO₂, CF₃, methyl, and ethyl;

R⁴¹, at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, =O,
30 C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴², and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group

consisting of N, O, and S substituted with 0-3
R⁴⁴;

R⁴², at each occurrence, is independently selected from
5 H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, SR⁴⁵, NR⁴⁶R⁴⁷, OR⁴⁸,
NO₂, CN, CH(=NH)NH₂, NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
C₃₋₆ cycloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
10 aryl substituted with 0-3 R⁴⁴, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴⁴;

15

R⁴³ is C₃₋₆ cycloalkyl or aryl substituted with 0-3 R⁴⁴;

R⁴⁴, at each occurrence, is independently selected from H,
halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂,
20 C₁₋₄ alkyl, and C₁₋₄ alkoxy;

R⁴⁵ is C₁₋₄ alkyl;

R⁴⁶, at each occurrence, is independently selected from H
25 and C₁₋₃ alkyl;

R⁴⁷, at each occurrence, is independently selected from H,
C₁₋₄ alkyl, -C(=O)NH(C₁₋₄ alkyl), -SO₂(C₁₋₄ alkyl),
-SO₂(phenyl), -C(=O)O(C₁₋₄ alkyl), -C(=O)(C₁₋₄ alkyl),
30 and -C(=O)H;

R⁴⁸, at each occurrence, is independently selected from H,
C₁₋₄ alkyl, -C(=O)NH(C₁₋₄ alkyl), -C(=O)O(C₁₋₄ alkyl),

-C(=O)(C₁₋₄ alkyl), and -C(=O)H;

k is 1 or 2;

5 m is 0, 1, 2; and

n is 1 or 2.

11. A compound of Claim 9 wherein:

10

X is -NR^{10A}-;

R¹ is selected from

- 15 C₂₋₄ alkyl substituted with Z,
C₂₋₄ alkenyl substituted with Z,
C₂₋₄ alkynyl substituted with Z,
C₃₋₆ cycloalkyl substituted with Z,
aryl substituted with Z,
5-6 membered heterocyclic ring system containing at
20 least one heteroatom selected from the group
consisting of N, O, and S, said heterocyclic ring
system substituted with Z;
C₂₋₄ alkyl substituted with 0-2 R², and
C₂₋₄ alkenyl substituted with 0-2 R²;

25

Z is selected from H,

- CH(OH)R²,
-C(ethylenedioxy)R²,
-OR²,
30 -SR²,
-NR²R³,
-C(O)R²,
-C(O)NR²R³,
-NR³C(O)R²,

-C(O)OR²,
-S(O)R²,
-S(O)₂R²,
-S(O)₂NR²R³, and -NR³S(O)₂R²;

5

R², at each occurrence, is independently selected from
phenyl substituted with 0-5 R⁴²;
C₃₋₁₀ carbocyclic residue substituted with 0-3 R⁴¹, and
5-10 membered heterocyclic ring system containing from
10 1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴¹;

R³, at each occurrence, is independently selected from
15 H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, and
C₁₋₄ alkoxy;

alternatively, R² and R³ join to form a 5- or 6-membered
ring optionally substituted with -O- or -N(R⁴)-;
20

R⁴, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;

R⁵ is H;
25

R^{6a} is selected from H, -OH, -CF₃, methyl, ethyl, propyl,
butyl, methoxy, and, ethoxy;

R^{6b} is H;
30

R⁷, R⁸, and R⁹, at each occurrence, are independently
selected from
H, halo, -CF₃, -OCF₃, -OH, -OCH₃, -CN, -NO₂,

C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, (C₁₋₃
haloalkyl)oxy, and
C₁₋₄ alkyl substituted with 0-2 R¹¹;

5 R^{10A} is selected from H, C₁₋₆ alkyl, C₁₋₄ alkoxy, and
C₁₋₂ alkyl substituted with 0-1 R^{10B};

R^{10B} is C₃₋₆ cycloalkyl or
phenyl substituted with 0-3 R³³;

10

R¹¹ is selected from
H, halo, -CF₃, -OCF₃, -OH, -OCH₃, -CN, -NO₂,
C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, and (C₁₋₃
haloalkyl)oxy;

15

R³³, at each occurrence, is independently selected from
H, OH, halo, CF₃, and methyl;

20 R⁴¹, at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, NR⁴⁶R⁴⁷, NO₂, CN, =O,
C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴², and
5-10 membered heterocyclic ring system containing from
25 1-4 heteroatoms selected from the group
consisting of N, O, and S substituted with 0-3
R⁴⁴;

30 R⁴², at each occurrence, is independently selected from
H, CF₃, halo, OH, CO₂H, SO₂R⁴⁵, SR⁴⁵, NR⁴⁶R⁴⁷, OR⁴⁸,
NO₂, CN, CH(=NH)NH₂, NHC(=NH)NH₂,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl,
C₃₋₆ cycloalkyl,

C₁₋₄ alkyl substituted with 0-1 R⁴³,
aryl substituted with 0-3 R⁴⁴, and
5-10 membered heterocyclic ring system containing from
1-4 heteroatoms selected from the group
5 consisting of N, O, and S substituted with 0-3
R⁴⁴;

R⁴³ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
phenyl, or pyridyl, each substituted with 0-3 R⁴⁴;

10

R⁴⁴, at each occurrence, is independently selected from H,
halo, -OH, NR⁴⁶R⁴⁷, CO₂H, SO₂R⁴⁵, -CF₃, -OCF₃, -CN, -NO₂,
methyl, ethyl, propyl, butyl, methoxy, ethoxy,
propoxy, and butoxy;

15

R⁴⁵ is methyl, ethyl, propyl, or butyl;

R⁴⁶, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;

20

R⁴⁷, at each occurrence, is independently selected from
H, methyl, ethyl, n-propyl, i-propyl, n-butyl,
i-butyl, -C(=O)NH(methyl), -C(=O)NH(ethyl),
-SO₂(methyl), -SO₂(ethyl), -SO₂(phenyl),
25 -C(=O)O(methyl), -C(=O)O(ethyl), -C(=O)(methyl),
-C(=O)(ethyl), and -C(=O)H;

R⁴⁸, at each occurrence, is independently selected from
H, methyl, ethyl, n-propyl, i-propyl, -
30 C(=O)NH(methyl), -C(=O)NH(ethyl), -C(=O)O(methyl), -
C(=O)O(ethyl), -C(=O)(methyl), -C(=O)(ethyl), and -
C(=O)H;

k is 1;

35

m is 0, 1, or 2; and

n is 1 or 2.

5 12. A compound of Claim 9 wherein:

X is -NH-;

R¹ is selected from

10 ethyl substituted with Z,
propyl substituted with Z,
butyl substituted with Z,
propenyl substituted with Z,
butenyl substituted with Z,
15 ethyl substituted with R²,
propyl substituted with R²,
butyl substituted with R²,
propenyl substituted with R², and
butenyl substituted with R²;

20

Z is selected from H,

-CH(OH)R²,
-OR²,
-SR²,
25 -NR²R³,
-C(O)R²,
-C(O)NR²R³,
-NR³C(O)R²,
-C(O)OR²,
30 -S(O)R²,
-S(O)₂R²,
-S(O)₂NR²R³, and -NR³S(O)₂R²;

R², at each occurrence, is independently selected from

- phenyl substituted with 0-3 R⁴²;
naphthyl substituted with 0-3 R⁴²;
cyclopropyl substituted with 0-3 R⁴¹;
cyclobutyl substituted with 0-3 R⁴¹;
5 cyclopentyl substituted with 0-3 R⁴¹;
cyclohexyl substituted with 0-3 R⁴¹;
pyridyl substituted with 0-3 R⁴¹;
indolyl substituted with 0-3 R⁴¹;
indolinyl substituted with 0-3 R⁴¹;
10 benzimidazolyl substituted with 0-3 R⁴¹;
benzotriazolyl substituted with 0-3 R⁴¹;
benzothienyl substituted with 0-3 R⁴¹;
benzofuranyl substituted with 0-3 R⁴¹;
phthalimid-1-yl substituted with 0-3 R⁴¹;
15 inden-2-yl substituted with 0-3 R⁴¹;
2,3-dihydro-1H-inden-2-yl substituted with 0-3 R⁴¹;
indazolyl substituted with 0-3 R⁴¹;
tetrahydroquinolinyl substituted with 0-3 R⁴¹; and
tetrahydro-isoquinolinyl substituted with 0-3 R⁴¹;
20
- R³, at each occurrence, is independently selected from
H, methyl, and ethyl;
- 25 R⁵ is H;
- R^{6a} is selected from H, -OH, methyl, and methoxy;
- R^{6b} is H;
- 30 R⁷, R⁸, and R⁹, at each occurrence, are independently
selected from H, F, Cl, methyl, ethyl, methoxy, -CF₃,
and -OCF₃;

R⁴¹, at each occurrence, is independently selected from
H, F, Cl, Br, OH, CF₃, NO₂, CN, =O, methyl, ethyl,
propyl, butyl, methoxy, and ethoxy;

5 R⁴², at each occurrence, is independently selected from
H, F, Cl, Br, OH, CF₃, SO₂R⁴⁵, SR⁴⁵, NR⁴⁶R⁴⁷, OR⁴⁸, NO₂,
CN, =O, methyl, ethyl, propyl, butyl, methoxy, and
ethoxy;

10 R⁴⁵ is methyl, ethyl, propyl, or butyl;

R⁴⁶, at each occurrence, is independently selected from H,
methyl, ethyl, propyl, and butyl;

15 R⁴⁷, at each occurrence, is independently selected from
H, methyl, ethyl, n-propyl, i-propyl, n-butyl,
i-butyl, -C(=O)NH(methyl), -C(=O)NH(ethyl),
-SO₂(methyl), -SO₂(ethyl), -SO₂(phenyl),
-C(=O)O(methyl), -C(=O)O(ethyl), -C(=O)(methyl),
20 -C(=O)(ethyl), and -C(=O)H;

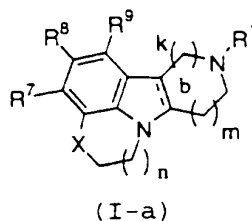
R⁴⁸, at each occurrence, is independently selected from
H, methyl, ethyl, n-propyl, i-propyl, -
C(=O)NH(methyl), -C(=O)NH(ethyl), -C(=O)O(methyl), -
25 C(=O)O(ethyl), -C(=O)(methyl), -C(=O)(ethyl), and -
C(=O)H;

k is 1;

30 m is 0, 1, or 2; and

n is 1 or 2.

13. A compound of Claim 9 of Formula (I-a)



wherein:

5

b is a single bond or a double bond;

X is -NR^{10A}-;

10 R¹ is selected from

-(CH₂)₃C(=O) (4-fluoro-phenyl),

-(CH₂)₃C(=O) (4-bromo-phenyl),

-(CH₂)₃C(=O) (4-methyl-phenyl),

-(CH₂)₃C(=O) (4-methoxy-phenyl),

15 -(CH₂)₃C(=O) (4-(3,4-dichloro-phenyl)phenyl),

-(CH₂)₃C(=O) (3-methyl-4-fluoro-phenyl),

-(CH₂)₃C(=O) (2,3-dimethoxy-phenyl),

-(CH₂)₃C(=O) (phenyl),

-(CH₂)₃C(=O) (4-chloro-phenyl),

20 -(CH₂)₃C(=O) (3-methyl-phenyl),

-(CH₂)₃C(=O) (4-t-butyl-phenyl),

-(CH₂)₃C(=O) (3,4-difluoro-phenyl),

-(CH₂)₃C(=O) (2-methoxy-5-fluoro-phenyl),

-(CH₂)₃C(=O) (4-fluoro-1-naphthyl),

25 -(CH₂)₃C(=O) (benzyl),

-(CH₂)₃C(=O) (4-pyridyl),

-(CH₂)₃C(=O) (3-pyridyl),

-(CH₂)₃CH(OH) (4-fluoro-phenyl),

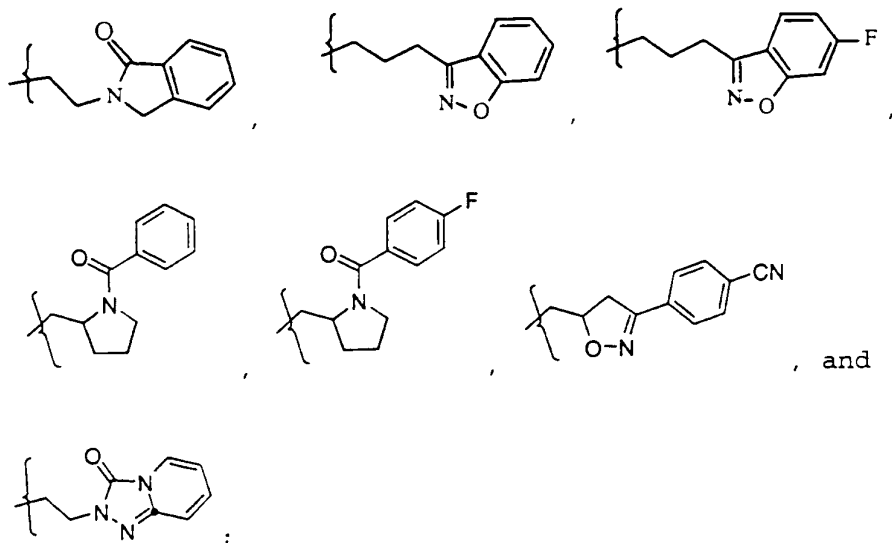
-(CH₂)₃CH(OH) (4-pyridyl),

30 -(CH₂)₃CH(OH) (2,3-dimethoxy-phenyl),

- (CH₂)₃S (3-fluoro-phenyl) ,
- (CH₂)₃S (4-fluoro-phenyl) ,
- (CH₂)₃S (=O) (4-fluoro-phenyl) ,
- (CH₂)₃SO₂ (3-fluoro-phenyl) ,
- 5 - (CH₂)₃SO₂ (4-fluoro-phenyl) ,
- (CH₂)₃O (4-fluoro-phenyl) ,
- (CH₂)₃O (phenyl) ,
- (CH₂)₃O (3-pyridyl) ,
- (CH₂)₃O (4-pyridyl) ,
- 10 - (CH₂)₃O (2-NH₂-phenyl) ,
- (CH₂)₃O (2-NH₂-5-F-phenyl) ,
- (CH₂)₃O (2-NH₂-4-F-phenyl) ,
- (CH₂)₃O (2-NH₂-3-F-phenyl) ,
- (CH₂)₃O (2-NH₂-4-Cl-phenyl) ,
- 15 - (CH₂)₃O (2-NH₂-4-OH-phenyl) ,
- (CH₂)₃O (2-NH₂-4-Br-phenyl) ,
- (CH₂)₃O (2-NHC (=O) Me-4-F-phenyl) ,
- (CH₂)₃O (2-NHC (=O) Me-phenyl) ,
- (CH₂)₃NH (4-fluoro-phenyl) ,
- 20 - (CH₂)₃N (methyl) (4-fluoro-phenyl) ,
- (CH₂)₃CO₂ (ethyl) ,
- (CH₂)₃C (=O) N (methyl) (methoxy) ,
- (CH₂)₃C (=O) NH (4-fluoro-phenyl) ,
- (CH₂)₂NHC (=O) (phenyl) ,
- 25 - (CH₂)₂NMeC (=O) (phenyl) ,
- (CH₂)₂NHC (=O) (2-fluoro-phenyl) ,
- (CH₂)₂NMeC (=O) (2-fluoro-phenyl) ,
- (CH₂)₂NHC (=O) (4-fluoro-phenyl) ,
- (CH₂)₂NMeC (=O) (4-fluoro-phenyl) ,
- 30 - (CH₂)₂NHC (=O) (2,4-difluoro-phenyl) ,
- (CH₂)₂NMeC (=O) (2,4-difluoro-phenyl) ,
- (CH₂)₃ (3-indolyl) ,
- (CH₂)₃ (1-methyl-3-indolyl) ,

- (CH₂)₃(1-indolyl),
- (CH₂)₃(1-indolinyl),
- (CH₂)₃(1-benzimidazolyl),
- (CH₂)₃(1H-1,2,3-benzotriazol-1-yl),
- 5 - (CH₂)₃(1H-1,2,3-benzotriazol-2-yl),
- (CH₂)₂(1H-1,2,3-benzotriazol-1-yl),
- (CH₂)₂(1H-1,2,3-benzotriazol-2-yl),
- (CH₂)₃(3,4 dihydro-1(2H)-quinolinyl),
- (CH₂)₂C(=O)(4-fluoro-phenyl),
- 10 - (CH₂)₂C(=O)NH(4-fluoro-phenyl),
- CH₂CH₂(3-indolyl),
- CH₂CH₂(1-phthalimidyl),
- (CH₂)₄C(=O)N(methyl)(methoxy),
- (CH₂)₄CO₂(ethyl),
- 15 - (CH₂)₄C(=O)(phenyl),
- (CH₂)₄(cyclohexyl),
- (CH₂)₃CH(phenyl)₂,
- CH₂CH₂CH=C(phenyl)₂,
- CH₂CH₂CH=CMe(4-F-phenyl),
- 20 - (CH₂)₃CH(4-fluoro-phenyl)₂,
- CH₂CH₂CH=C(4-fluoro-phenyl)₂,
- (CH₂)₂(2,3-dihydro-1H-inden-2-yl),
- (CH₂)₃C(=O)(2-NH₂-phenyl),
- (CH₂)₃C(=O)(2-NH₂-5-F-phenyl),
- 25 - (CH₂)₃C(=O)(2-NH₂-4-F-phenyl),
- (CH₂)₃C(=O)(2-NH₂-3-F-phenyl),
- (CH₂)₃C(=O)(2-NH₂-4-Cl-phenyl),
- (CH₂)₃C(=O)(2-NH₂-4-OH-phenyl),
- (CH₂)₃C(=O)(2-NH₂-4-Br-phenyl),
- 30 - (CH₂)₃(1H-indazol-3-yl),
- (CH₂)₃(5-F-1H-indazol-3-yl),
- (CH₂)₃(7-F-1H-indazol-3-yl),
- (CH₂)₃(6-Cl-1H-indazol-3-yl),

- (CH₂)₃ (6-Br-1H-indazol-3-yl),
- (CH₂)₃ C(=O) (2-NHMe-phenyl),
- (CH₂)₃ (1-benzothien-3-yl),
- (CH₂)₃ (6-F-1H-indol-1-yl),
- 5 - (CH₂)₃ (5-F-1H-indol-1-yl),
- (CH₂)₃ (6-F-2,3-dihydro-1H-indol-1-yl),
- (CH₂)₃ (5-F-2,3-dihydro-1H-indol-1-yl),
- (CH₂)₃ (6-F-1H-indol-3-yl),
- (CH₂)₃ (5-F-1H-indol-3-yl),
- 10 - (CH₂)₃ (5-F-1H-indol-3-yl),
- (CH₂)₃ (9H-purin-9-yl),
- (CH₂)₃ (7H-purin-7-yl),
- (CH₂)₃ (6-F-1H-indazol-3-yl),
- (CH₂)₃ C(=O) (2-NHSO₂Me-4-F-phenyl),
- 15 - (CH₂)₃ C(=O) (2-NHC(=O)Me-4-F-phenyl),
- (CH₂)₃ C(=O) (2-NHC(=O)Me-phenyl),
- (CH₂)₃ C(=O) (2-NHCO₂Et-4-F-phenyl),
- (CH₂)₃ C(=O) (2-NHC(=O)NH₂-4-F-phenyl),
- (CH₂)₃ C(=O) (2-NHCHO-4-F-phenyl),
- 20 - (CH₂)₃ C(=O) (2-OH-4-F-phenyl),
- (CH₂)₃ C(=O) (2-MeS-4-F-phenyl),
- (CH₂)₃ C(=O) (2-NHSO₂Me-4-F-phenyl),
- (CH₂)₂ C(Me)CO₂Me,
- (CH₂)₂ C(Me)CH(OH) (4-F-phenyl)₂,
- 25 - (CH₂)₂ C(Me)CH(OH) (4-Cl-phenyl)₂,
- (CH₂)₂ C(Me)C(=O) (4-F-phenyl),
- (CH₂)₂ C(Me)C(=O) (2-MeO-4-F-phenyl),
- (CH₂)₂ C(Me)C(=O) (3-Me-4-F-phenyl),
- (CH₂)₂ C(Me)C(=O) (2-Me-phenyl),
- 30 - (CH₂)₂ C(Me)C(=O)phenyl,



R^7 , R^8 , and R^9 , at each occurrence, are independently selected from

hydrogen, fluoro, chloro, bromo, cyano, methyl, ethyl,
 10 propyl, isopropyl, butyl, t-butyl, nitro,
 trifluoromethyl, methoxy, ethoxy, isopropoxy,
 trifluoromethoxy, phenyl, benzyl,

$HC(=O)-$, $methylC(=O)-$, $ethylC(=O)-$, $propylC(=O)-$,
 15 $isopropylC(=O)-$, $n-butylC(=O)-$, $isobutylC(=O)-$,
 $secbutylC(=O)-$, $tertbutylC(=O)-$, $phenylC(=O)-$,

$methylC(=O)NH-$, $ethylC(=O)NH-$, $propylC(=O)NH-$,
 20 $isopropylC(=O)NH-$, $n-butylC(=O)NH-$, $isobutylC(=O)NH-$,
 $secbutylC(=O)NH-$, $tertbutylC(=O)NH-$, $phenylC(=O)NH-$,

$methylamino-$, $ethylamino-$, $propylamino-$, $isopropylamino-$,
 25 $n-butylamino-$, $isobutylamino-$, $secbutylamino-$,
 $tertbutylamino-$, $phenylamino-$,

provided that two of substituents R^7 , R^8 , and R^9 , are
 independently selected from hydrogen, fluoro, chloro,

bromo, cyano, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, nitro, trifluoromethyl, methoxy, ethoxy, isopropoxy, and trifluoromethoxy;

5 R^{10A} is selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, benzyl, 2-chlorobenzyl, 2-fluorobenzyl, 2-bromobenzyl, 2-methylbenzyl, 2-trifluoromethylbenzyl, 2-methoxybenzyl, 2-trifluoromethoxybenzyl, 3-chlorobenzyl, 3-fluorobenzyl, 3-bromobenzyl, 3-methylbenzyl, 3-trifluoromethylbenzyl, 3-methoxybenzyl, 3-trifluoromethoxybenzyl, 4-chlorobenzyl, 4-fluorobenzyl, 4-bromobenzyl, 4-methylbenzyl, 4-trifluoromethylbenzyl, 4-methoxybenzyl, and 4-trifluoromethoxybenzyl;

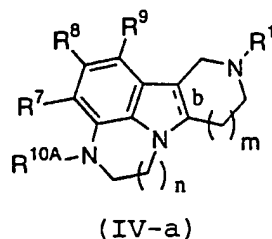
k is 1 or 2;

m is 1 or 2; and

n is 1 or 2.

20

14. A compound of Claim 13 of Formula (IV-a)



25

wherein:

b is a single bond, wherein the bridge hydrogens are in a cis position;

30

R¹ is selected from

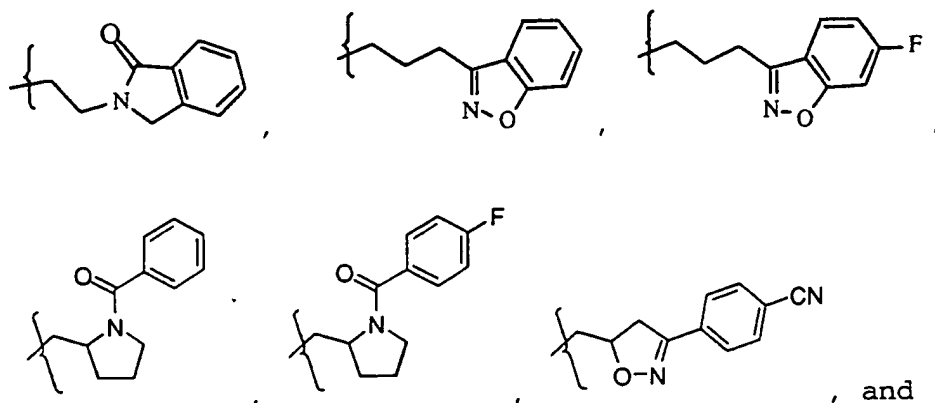
-(CH₂)₃C(=O)(4-fluoro-phenyl),

- (CH₂)₃C(=O) (4-bromo-phenyl),
- (CH₂)₃C(=O) (4-methyl-phenyl),
- (CH₂)₃C(=O) (4-methoxy-phenyl),
- (CH₂)₃C(=O) (4- (3,4-dichloro-phenyl)phenyl),
- 5 - (CH₂)₃C(=O) (3-methyl-4-fluoro-phenyl),
- (CH₂)₃C(=O) (2,3-dimethoxy-phenyl),
- (CH₂)₃C(=O) (phenyl),
- (CH₂)₃C(=O) (4-chloro-phenyl),
- (CH₂)₃C(=O) (3-methyl-phenyl),
- 10 - (CH₂)₃C(=O) (4-t-butyl-phenyl),
- (CH₂)₃C(=O) (3,4-difluoro-phenyl),
- (CH₂)₃C(=O) (2-methoxy-5-fluoro-phenyl),
- (CH₂)₃C(=O) (4-fluoro-1-naphthyl),
- (CH₂)₃C(=O) (benzyl),
- 15 - (CH₂)₃C(=O) (4-pyridyl),
- (CH₂)₃C(=O) (3-pyridyl),
- (CH₂)₃CH(OH) (4-fluoro-phenyl),
- (CH₂)₃CH(OH) (4-pyridyl),
- (CH₂)₃CH(OH) (2,3-dimethoxy-phenyl),
- 20 - (CH₂)₃S(3-fluoro-phenyl),
- (CH₂)₃S(4-fluoro-phenyl),
- (CH₂)₃S(=O) (4-fluoro-phenyl),
- (CH₂)₃SO₂ (3-fluoro-phenyl),
- (CH₂)₃SO₂ (4-fluoro-phenyl),
- 25 - (CH₂)₃O(4-fluoro-phenyl),
- (CH₂)₃O(phenyl) ,
- (CH₂)₃NH(4-fluoro-phenyl),
- (CH₂)₃N(methyl) (4-fluoro-phenyl),
- (CH₂)₃CO₂ (ethyl),
- 30 - (CH₂)₃C(=O)N(methyl) (methoxy),
- (CH₂)₃C(=O)NH(4-fluoro-phenyl),
- (CH₂)₂NHC(=O) (phenyl),
- (CH₂)₂NMeC(=O) (phenyl),

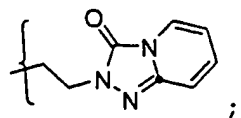
- (CH₂)₂NHC(=O) (2-fluoro-phenyl) ,
- (CH₂)₂NMeC(=O) (2-fluoro-phenyl) ,
- (CH₂)₂NHC(=O) (4-fluoro-phenyl) ,
- (CH₂)₂NMeC(=O) (4-fluoro-phenyl) ,
- 5 - (CH₂)₂NHC(=O) (2,4-difluoro-phenyl) ,
- (CH₂)₂NMeC(=O) (2,4-difluoro-phenyl) ,
- (CH₂)₃ (3-indolyl) ,
- (CH₂)₃ (1-methyl-3-indolyl) ,
- (CH₂)₃ (1-indolyl) ,
- 10 - (CH₂)₃ (1-indoliny) ,
- (CH₂)₃ (1-benzimidazolyl) ,
- (CH₂)₃ (1H-1,2,3-benzotriazol-1-yl) ,
- (CH₂)₃ (1H-1,2,3-benzotriazol-2-yl) ,
- (CH₂)₂ (1H-1,2,3-benzotriazol-1-yl) ,
- 15 - (CH₂)₂ (1H-1,2,3-benzotriazol-2-yl) ,
- (CH₂)₃ (3,4 dihydro-1(2H)-quinoliny) ,
- (CH₂)₂C(=O) (4-fluoro-phenyl) ,
- (CH₂)₂C(=O)NH (4-fluoro-phenyl) ,
- CH₂CH₂ (3-indolyl) ,
- 20 - CH₂CH₂ (1-phthalimidyl) ,
- (CH₂)₄C(=O)N(methyl) (methoxy) ,
- (CH₂)₄CO₂ (ethyl) ,
- (CH₂)₄C(=O) (phenyl) ,
- (CH₂)₄ (cyclohexyl) ,
- 25 - (CH₂)₃CH (phenyl)₂ ,
- CH₂CH₂CH=C (phenyl)₂ ,
- CH₂CH₂CH=CMe (4-F-phenyl) ,
- (CH₂)₃CH (4-fluoro-phenyl)₂ ,
- CH₂CH₂CH=C (4-fluoro-phenyl)₂ ,
- 30 - (CH₂)₂ (2,3-dihydro-1H-inden-2-yl) ,
- (CH₂)₃C(=O) (2-NH₂-phenyl) ,
- (CH₂)₃C(=O) (2-NH₂-5-F-phenyl) ,
- (CH₂)₃C(=O) (2-NH₂-4-F-phenyl) ,

- (CH₂)₃C(=O) (2-NH₂-3-F-phenyl),
- (CH₂)₃C(=O) (2-NH₂-4-Cl-phenyl),
- (CH₂)₃C(=O) (2-NH₂-4-OH-phenyl),
- (CH₂)₃C(=O) (2-NH₂-4-Br-phenyl),
- 5 - (CH₂)₃ (1H-indazol-3-yl),
- (CH₂)₃ (5-F-1H-indazol-3-yl),
- (CH₂)₃ (7-F-1H-indazol-3-yl),
- (CH₂)₃ (6-Cl-1H-indazol-3-yl),
- (CH₂)₃ (6-Br-1H-indazol-3-yl),
- 10 - (CH₂)₃C(=O) (2-NHMe-phenyl),
- (CH₂)₃ (1-benzothien-3-yl),
- (CH₂)₃ (6-F-1H-indol-1-yl),
- (CH₂)₃ (5-F-1H-indol-1-yl),
- (CH₂)₃ (6-F-2,3-dihydro-1H-indol-1-yl),
- 15 - (CH₂)₃ (5-F-2,3-dihydro-1H-indol-1-yl),
- (CH₂)₃ (6-F-1H-indol-3-yl),
- (CH₂)₃ (5-F-1H-indol-3-yl),
- (CH₂)₃ (5-F-1H-indol-3-yl),
- (CH₂)₃ (9H-purin-9-yl),
- 20 - (CH₂)₃ (7H-purin-7-yl),
- (CH₂)₃ (6-F-1H-indazol-3-yl),
- (CH₂)₃C(=O) (2-NHSO₂Me-4-F-phenyl),
- (CH₂)₃C(=O) (2-NHC(=O)Me-4-F-phenyl),
- (CH₂)₃C(=O) (2-NHC(=O)Me-4-F-phenyl),
- 25 - (CH₂)₃C(=O) (2-NHCO₂Et-4-F-phenyl),
- (CH₂)₃C(=O) (2-NHC(=O)NH₂-4-F-phenyl),
- (CH₂)₃C(=O) (2-NHCHO-4-F-phenyl),
- (CH₂)₃C(=O) (2-OH-4-F-phenyl),
- (CH₂)₃C(=O) (2-MeS-4-F-phenyl),
- 30 - (CH₂)₃C(=O) (2-NHSO₂Me-4-F-phenyl),
- (CH₂)₂C(Me)CO₂Me,
- (CH₂)₂C(Me)CH(OH) (4-F-phenyl)₂,
- (CH₂)₂C(Me)CH(OH) (4-Cl-phenyl)₂,

- (CH₂)₂C(Me)C(=O) (4-F-phenyl) ,
 - (CH₂)₂C(Me)C(=O) (2-MeO-4-F-phenyl) ,
 - (CH₂)₂C(Me)C(=O) (3-Me-4-F-phenyl) ,
 - (CH₂)₂C(Me)C(=O) (2-Me-phenyl) ,
 5 - (CH₂)₂C(Me)C(=O)phenyl ,



10



- R⁷, R⁸, and R⁹, at each occurrence, are independently
 selected from hydrogen, fluoro, chloro, bromo, cyano,
 15 methyl, ethyl, propyl, isopropyl, butyl, t-butyl,
 nitro, trifluoromethyl, methoxy, ethoxy, isopropoxy,
 trifluoromethoxy, methylC(=O)-, ethylC(=O)-,
 propylC(=O)-, isopropylC(=O)-, methylC(=O)NH-,
 ethylC(=O)NH -, propylC(=O)NH-, isopropylC(=O)NH,
 20 methylamino-, ethylamino-, propylamino-, and
 isopropylamino-,

- provided that two of substituents R⁷, R⁸, and R⁹, are
 independently selected from hydrogen, fluoro, chloro,
 25 methyl, trifluoromethyl, methoxy, and trifluoromethoxy;

R^{10A} is selected from hydrogen, methyl, ethyl, propyl, isopropyl, butyl, benzyl, 2-chlorobenzyl, 2-fluorobenzyl, 2-bromobenzyl, 2-methylbenzyl, 2-trifluoromethylbenzyl, 2-methoxybenzyl, 2-trifluoromethoxybenzyl, 3-chlorobenzyl, 3-fluorobenzyl, 3-bromobenzyl, 3-methylbenzyl, 3-trifluoromethylbenzyl, 3-methoxybenzyl, 3-trifluoromethoxybenzyl, 4-chlorobenzyl, 4-fluorobenzyl, 4-bromobenzyl, 4-methylbenzyl, 4-trifluoromethylbenzyl, 4-methoxybenzyl, and 4-trifluoromethoxybenzyl;

m is 1 or 2; and

n is 1 or 2.

15

15. A compound of Claim 1 selected from the group consisting of compounds disclosed in Table 1.

20 16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to one of Claims 1-15, or a pharmaceutically acceptable salt thereof.

25 17. A method for treating a human suffering from a disorder associated with 5HT_{2C} receptor modulation comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to one of Claims 1-8, or a pharmaceutically acceptable salt
30 thereof.

18. A method of Claim 17 for treating a human suffering from a disorder associated with 5HT_{2c} receptor modulation wherein the compound is a 5HT_{2C} agonist.

35

19. A method for treating a human suffering from a disorder associated with 5HT2A receptor modulation comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to one of Claims 1 or 9-14, or a pharmaceutically acceptable salt thereof.

20. A method of Claim 19 for treating a human suffering from a disorder associated with 5HT2A receptor modulation wherein the compound is a 5HT2A antagonist.

21. A method for treating obesity comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to one of Claims 1-15, or a pharmaceutically acceptable salt thereof.

22. A method for treating schizophrenia comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to one of Claims 1-15, or a pharmaceutically acceptable salt thereof.

23. A method for treating depression comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to one of Claims 1-15, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Int. J. Appl. No.
PCT/US 00/16498

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/16 A61K31/554 A61K31/4985 A61K31/5517 A61P25/00
C07D487/16 //(C07D471/16,241:00,221:00,209:00),(C07D471/16,
243:00,221:00,209:00),(C07D487/16,241:00,223:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 213 283 A (INST IM ORDZHONIKIDZE) 2 August 1974 (1974-08-02) page 2, line 18 - line 27; claim 1 ----	1,16
A	US 4 219 550 A (RAJAGOPALAN PARTHASARATHI) 26 August 1980 (1980-08-26) cited in the application claims 1,15 -----	1,16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

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O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Z document member of the same patent family

Date of the actual completion of the international search

28 November 2000

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06/12/2000

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INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2213283 A	02-08-1974	NONE	
US 4219550 A	26-08-1980	NONE	